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(54) Title: NOVEL PRODUCT AND PROCESS FOR T LYMPHOCYTE VETO

(57) Abstract

The present invention relates to a product and process for suppressing an immune response using a T lymphocyte veto molecule capable of blocking cell surface molecules responsible for T cell activation. Disclosed is a CD4 or CD2 molecule, associated with an immunoglobulin molecule capable of binding to a major histocompatibility antigen. Also disclosed is a method to produce a T lymphocyte veto molecule, a therapeutic composition comprising a T lymphocyte veto molecule and methods to use T lymphocyte veto molecules in therapeutic processes requiring suppression of an immune response.

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NOVEL PRODUCT AND PROCESS FOR T LYMPHOCYTE VETO

GOVERNMENT RIGHTS

This invention was made in part with government support under AI35194, awarded by the National Institutes of Health. The government has certain rights to this invention.

FIELD OF THE INVENTION

The present invention relates to a product and process for immunosuppression of subjects having undesired immunological reactivities and in subjects in need of cell, tissue or organ transplant survival. More particularly, the present invention relates to a T lymphocyte veto molecule (hereinafter defined) and the use of such a molecule as an immunoregulator to effect therapeutic objectives.

BACKGROUND OF THE INVENTION

A wide variety of medical treatments require regulation of the immune response in a patient. Such treatments include, for example, vaccinations, treatments for autoimmune diseases, immunodeficiency diseases, immunoproliferative diseases and treatments involving the transplantation of organs and skin. Traditional reagents and methods used to regulate a subject's immune response often results in unwanted side effects. For example, immunosuppressive reagents such as cyclosporin A, azathioprine and prednisone are used to suppress the immune

system of a patient with an autoimmune disease or patients receiving transplants. Such reagents, however, suppress a patient's entire immune response, thereby crippling the ability of the patient to mount an immune response against infectious agents not involved in the original disease. Due to such harmful side effects and the medical importance of immune regulation, reagents and methods to regulate specific parts of the immune system have been the subject of study for many years.

Introduction of an antigen into a host initiates a series of events culminating in an immune response. In addition, self-antigens can result in immunological tolerance or activation of an immune response against self-antigens. A major portion of the immune response is regulated by the interaction of a stimulator cell (defined in detail below) with a responding cell (defined in detail below).

Particular reagents having immunoregulatory potential of cell to cell interactions have been suggested by various investigators. Tykocinski et al. disclose in U.S. Patent No. 5,242,687, issued Sep. 7, 1993, a composition comprising a CD8 peptide associated with a secondary ligand, including an Fc domain of immunoglobulin or a major histocompatibility molecule (MHC). Tykocinski et al. do not teach or suggest such a composition involving CD4, CD2, CD28, CTLA4 or fas-ligand proteins which are known to have

significantly different functions in various immunity mechanisms.

In U.S. Patent No. 5,336,603, issued Aug. 9, 1994, Capon et al. disclose "immunoadhesons" useful for immunomodulatory therapy. Capon et al. disclose adhesons as cell surface polypeptides, examples of which include CD8, CD4 and CD2, that can be combined with an immunologically active non-adheson polypeptide. Capon et al., however, do not teach or suggest a T cell veto molecule useful for immunosuppression and particularly a molecule that prevents the specific activation of responding cells by stimulator cells to suppress an immune response.

As such, there remains a need for therapeutic reagents and strategies that suppress an immune response in a safe and effective manner.

SUMMARY

The present invention relates to a novel product and process for treatment of subjects in need of the abrogation of immunological reactivities. According to the present invention there are provided soluble or membrane-bound T lymphocyte veto molecules for immunosuppression *in vivo* or *in vitro*. The present invention overcomes traditional problems with immunoregulatory reagents by specifically regulating stimulator cell activation of responding cells capable of killing transplanted cells or capable of responding to autoantigens. This act of regulation is

referred to herein as T cell veto. A molecule capable of T cell veto is referr d to herein as a T cell veto molecule. In addition, the immunoregulatory reagents of the present invention can be administered locally, thereby alleviating problems that arise from extensive immunosuppression in an animal.

More specifically, one embodiment of the present invention includes a T lymphocyte veto molecule which includes a chimeric molecule having a protein selected from the group consisting of CD4 protein, CD2 protein, CD28 protein, CTLA4 protein, Fas-ligand protein, CD5 protein, CD7 protein, CD9 protein, CD11 protein, CD18 protein, CD27 protein, CD43 protein, CD45 protein, CD48 protein, B7.1 protein and B7.2 protein. The protein is linked to a targeting polypeptide that binds to a molecule that differentiates a host cell from a tissue graft cell. A further embodiment of the present invention is a T lymphocyte veto molecule which includes a chimeric molecule having one of such proteins. In this embodiment, the protein is linked to a targeting polypeptide that binds to a molecule which selectively targets a stimulator cell involved in an autoimmune response. In further aspects of these embodiments, the targeting polypeptide can be an immunoglobulin molecule, a growth factor or a tissue specific antigen. Such T lymphocyte veto molecules can be included in therapeutic compositions which also include pharmaceutically acceptable carriers.

A further embodiment of the present invention includes a recombinant cell, which has a first recombinant molecule having a nucleic acid molecule operatively linked to an expression vector, wherein the nucleic acid molecule has a sequence which encodes one of the proteins mentioned above. The recombinant cell further includes a second recombinant molecule having a nucleic acid molecule operatively linked to an expression vector wherein the nucleic acid molecule encodes a protein which is a targeting molecule that differentiates between a host cell and a tissue graft cell.

A further aspect of the present invention includes a method for producing a T lymphocyte veto molecule. This method includes providing a first protein as mentioned above, providing a second protein which is a targeting molecule that differentiates a host cell from a tissue graft cell, and linking the first protein to the second protein to form a chimeric molecule.

The present invention also includes a method to suppress an immune response which includes exposing chimeric molecules of the present invention to a stimulator cell that can interact specifically with the chimeric molecule under conditions for reduction of an immune response.

A further aspect of the present invention is a method to alleviate tissue transplant rejection. This method includes administering to an animal an effective amount of

a therapeutic composition which includes a T lymphocyte veto molecule of the present invention.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 shows the results of an experiment in which a T lymphocyte veto molecule is capable of specifically inhibiting the proliferation of CD4+ responder T cells.

Fig. 2 shows the results of an experiment in which a T lymphocyte veto molecule of the present invention is capable of specifically inhibiting the production of IL-2 and IL-4 by CD4+ responder T cells.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a therapeutic reagent and process for treatment of subjects in need of the abrogation of immunological reactivities. The reagents and processes of the present invention are applicable to, but not limited to, the clinical settings of transplantation and autoimmunity, allergic disorders and other immunological disorders. Embodiments of the present invention include a novel T lymphocyte veto (TLV) molecule, also referred to herein as a T cell veto molecule, that regulates the activation of a responding cell by a stimulator cell, thereby suppressing an immune response. In a particular embodiment, a T cell veto molecule of the present invention is capable of specifically regulating the activation of one type of responding cell without

regulating or affecting the activation of other types of responding cells.

As used herein, a stimulator cell includes any cell that, under appropriate conditions, binds to a responding cell in such a manner that the responding cell is either activated, anergized or killed. Traditional stimulator cells include "professional" antigen presenting cells (APC; e.g., dendritic cells, macrophages and B cells). According to the present invention, stimulator cells can also include a cell having a T cell veto molecule of the present invention on its surface by, for example, a tissue graft cell-specific antibody. A stimulator cell can also include a tissue graft cell, including allogeneic and xenogeneic tissue graft cells. Such graft cells can include, for example, T lymphocyte (also referred to herein as a T cell).

A responding cell includes any cell capable of being activated by a stimulator cell. Traditional responding cells include CD4-CD8+ (CD8+), CD4+CD8+, CD4-CD8-, CD4+CD8- (CD4+), αβ and γδ T cells. According to the present invention, responding cells can also include B lymphocytes (also referred to herein as B cells), as well as "naive" or "precursor" T cells. As used herein, a "naive" T cell refers to a T cell that is not activated by a T cell veto molecule of the present invention when tested using a standard effector T cell assay, such as by cytotoxic T cell (CTL) assays, T cell proliferation assays, interleukin

secretion assays and assays measuring cell death (e.g., apoptosis assays). Pref rably, a responding cell of the present invention includes a T cell, in particular a naive CD4+ or CD8+ T cell.

Activation of a responding cell refers to induction of signal transduction pathways in the responding cell resulting in production of cellular products (e.g., interleukin-2) by that cell. Anergy refers to the diminished reactivity by a responding cell.

Embodiments of the present invention include a novel T cell veto molecule having at least two components: (1) a responding cell activating protein (RCA protein; as defined below); and (2) a stimulator cell marker molecule (SCM molecule; as defined below) that differentiates a stimulator cell from a responding cell, in one embodiment, a host cell from a tissue graft cell. As used herein, the term "targeting polypeptide" is synonymous with the term SCM molecule. The two components of a T cell veto molecule of the present invention are associated with each other, such as by being linked by chemical or peptide binds (described in detail below).

As noted, a T cell veto molecule of the present invention comprises an RCA protein an SCM molecule. It should be noted that reference herein to an RCA protein, an SCM molecule or specific embodiments thereof, such as a CD4 protein in the case of an RCA protein, refers to the full length protein or molecule as well as a portion of a

protein or molecule (e.g., non-protein with similar binding characteristics) that is at least sufficient to have the functional aspects of the referenced protein or molecule. Therefore, such a reference can refer to a full-length or partial polypeptide sequence that is capable of performing a desired function. For example, reference to a "CD4 protein" includes any portion of a CD4 molecule that is capable of binding to a CD4 co-receptor under conditions in which a complete CD4 protein binds to a co-receptor, and is capable of being linked to an SCM molecule. Similarly, a "CD2 protein" includes any portion of a CD2 molecule that is capable of binding to a CD2 co-receptor under conditions in which a complete CD2 protein binds to a co-receptor, and is capable of being linked to an SCM molecule. In addition, an SCM molecule includes any portion of a specific SCM molecule that is capable of binding to a molecule on the surface of a cell under conditions in which a complete SCM molecule would bind to a molecule on the surface of a cell, and is capable of being linked to an RCA protein of the present invention.

An RCA protein and an SCM molecule useful for the present invention is derived from an animal including, but not limited to, a human, a non-human primate, a pig, a mouse, a rat, a hamster, a rabbit, a horse and a goat, and preferably a human, a baboon and a pig.

A suitable RCA protein of the present invention comprises a protein that is capable of interfacing with a

stimulator cell activating a responding cell in such manner that the action of the resp nding cell is altered. The resulting action of the responding cell can be inability of the responding cell to bind to a stimulator cell, apoptosis or anergy. According to the present invention, an RCA protein is preferably able to regulate the activity of a T lymphocyte, more preferably a cytotoxic and helper T lymphocyte. In a further embodiment, an RCA protein is able to regulate the activity of a specific type of responder cell without regulating the activity of another type of responder cell. In a preferred embodiment, an RCA protein is able to regulate the activity of a $CD4^+$ T cell without regulating the activity of a $CD8^+$ T cell.

One embodiment of a responding cell activation protein of the present invention comprises a CD4 protein having one variable (V) and one constant (C2) domain. A CD4 protein of the present invention preferably comprises first and second V domains and first and second C2 domains of CD4. A CD4 protein of the present invention more preferably comprises the amino acid sequence extending from about residue 1 to about residue 203 of a processed human CD4, in which the initiating Met is residue 1. For human CD4 coding sequence, see Parnes, 1989, *Adv. Immunol.* 44: 265-311; Genbank M12807; and Swissprot P01730. A CD4 protein of the present invention even more preferably comprises the amino acid sequence disclosed in SEQ ID NO:1 and a leader sequence. A preferred leader sequence to be

used with a CD4 prot in of the present invention is disclosed in SEQ ID NO:29.

According t the present invention, a leader sequence is an amino acid sequence that naturally occurs at the amino terminus of a protein and functions to target the protein to a membrane for secretion. A leader sequence of the present invention can also be synthesized or isolated independently of the amino acid sequence with which the leader sequence naturally occurs. It should be noted that leader sequences of the present invention can be used with the protein with which the leader sequence naturally occurs (for example, a CD4 leader sequence with a CD4 protein), or can be interchanged with another leader sequence, including any of the leader sequences presented herein or other known leader sequences as will be known to those skilled in the art. It should also be noted that leader sequences of the present invention can be inserted anywhere into the amino acid sequences of RCA proteins of the present invention, provided that the functions of the leader sequence and the RCA are preserved.

Another embodiment of a responding cell activation protein of the present invention includes a CD2 protein having one extracellular domain of CD2 protein. A CD2 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 208 of CD2 protein, in which the initiating Met is residue 1. For human CD2 coding sequence, see Moingean et

al., 1989, *Immunol. Rev.* 111: 111-144; Genbank M16445; and Swissprot P06729. A CD2 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:2 and a leader sequence. A preferred leader sequence to be used with a CD2 protein of the present invention is disclosed in SEQ ID NO:30.

Another embodiment of a responding cell activation protein of the present invention includes a CD28 protein having a homodimer of the pseudo-V-region of CD28 protein. A CD28 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 161 of CD28 protein, in which the initiating Met is residue 1. For human CD28 coding sequence, see Aruffo et al., 1987, *Proc. Nat. Acad. Sci. USA* 84: 8573-8577; Genbank J02988; and Swissprot P10747. A CD28 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:3 and a leader sequence. A preferred leader sequence to be used with a CD28 protein of the present invention is disclosed in SEQ ID NO:31.

Another embodiment of a responding cell activation protein of the present invention includes a cytotoxic T cell antigen 4 (CTLA4) protein having a homodimer of the pseudo V region of CTLA4 protein. A CTLA4 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 161 of CTLA4 protein, in which the initiating Met is

residue 1. For human CTLA4 coding sequence, see Danavach et al., 1988, *Eur. J. Immunol.* 18: 1901-1905; Genbank X15070; and Swissprot P16410. A CTLA4 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:4 and a leader sequence. A preferred leader sequence to be used with a CTLA4 protein of the present invention is disclosed in SEQ ID NO:32.

Another embodiment of a responding cell activation protein of the present invention includes a fas-ligand protein having the extracellular domain of fas-ligand protein. A fas-ligand protein of the present invention preferably comprises the amino acid sequence extending from about residue 137 to about residue 283 of fas-ligand protein, in which the initiating Met is residue 1. For human fas-ligand coding sequence, see Takahashi et al., 1994, *Intern. Immunol.* 6: 1567-1574. A fas-ligand protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:5 and a leader sequence. An acceptable leader sequence to be used with a Fas-ligand protein of the present invention is disclosed, for example, in SEQ ID NO:29.

Another embodiment of a responding cell activation protein of the present invention includes a CD5 protein having the domains 1 through 3 of CD5 protein. A CD5 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 372 of CD5 protein, in which the initiating Met is

residue 1. For human CD5 coding sequence, see Jones et al., 1986, *Nature* 323: 346-349. A CD5 protein f the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:6 and a leader sequence. A preferred leader sequence to be used with a CD5 protein of the present invention is disclosed in SEQ ID NO:33.

Another embodiment of a responding cell activation protein of the present invention includes a CD7 protein having the pseudo V region of CD7 protein. A CD7 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 180 of CD7 protein, in which the initiating Met is residue 1. For human CD7 coding sequence, see Aruffo et al., 1987, *EMBO J.* 6: 3313-3316; Genbank X06180; and Swissprot P09564. A CD7 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:7 and a leader sequence. A preferred leader sequence to be used with a CD7 protein of the present invention is disclosed in SEQ ID NO:34.

Another embodiment of a responding cell activation protein of the present invention includes a CD9 protein having the extracellular domain of CD9 protein. A CD9 protein of the present invention preferably comprises the amino acid sequence extending from about residue 113 to about residue 192 of CD9 protein, in which the initiating Met is residue 1. For human CD9 coding sequence, see Boucheix et al., 1990, *J. Biol. Chem.* 266: 117-122; Genbank

M38690; and Swissprot P21926. A CD9 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:8 and a lead r sequence. An acceptable leader sequence to be used with a CD9 protein of the present invention is disclosed, for example, in SEQ ID NO:29.

Another embodiment of a responding cell activation protein of the present invention includes a CD11 protein having the CD11 alpha extracellular domain complexed with the CD18 extracellular domain of the CD11 protein. A CD11 alpha protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 1089 of CD11 alpha protein, in which the initiating Met is residue 1. For human CD11 alpha coding sequence, see Larson et al., 1990, *Immunol. Rev.* 114: 181-217; Genbank Y00796; and Swissprot P20701. A CD11 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:9 and a leader sequence. A preferred leader sequence to be used with a CD11 protein of the present invention is disclosed in SEQ ID NO:35.

Another embodiment of a responding cell activation protein of the present invention includes a CD18 protein having the extracellular domain of CD18 protein. A CD18 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 750 of CD18 protein, in which the initiating Met is

residue 1. For human CD18 coding sequence, see Larson et al., 1990, *Immunol. Rev.* 114: 181-217; G nbank Y00057; and Swissprot P05107. A CD18 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:10 and a leader sequence. A preferred leader sequence to be used with a CD18 protein of the present invention is disclosed in SEQ ID NO:36.

Another embodiment of a responding cell activation protein of the present invention includes a CD27 protein having the extracellular domain of CD27 protein. A CD27 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 191 of CD27 protein, in which the initiating Met is residue 1. For human CD27 coding sequence, see Camerinin et al., 1991, *J. Immunol.* 147: 3165-3169; Genbank M62928. A CD27 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:11 and a leader sequence. A preferred leader sequence to be used with a CD27 protein of the present invention is disclosed in SEQ ID NO:37.

Another embodiment of a responding cell activation protein of the present invention includes a CD43 protein having the extracellular domain of CD43 protein. A CD43 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 384 of CD43 protein, in which the initiating Met is residue 1. For human CD43 coding sequence, see Pallant et

al., 1989, *Proc. Nat. Acad. Sci. USA* 86: 1328-1332; Genbank J04168; and Swissprot 16150. A CD43 protein of the present invention mor preferably comprises the amino acid sequence disclosed in SEQ ID NO:12 and a leader sequence. A preferred leader sequence to be used with a CD43 protein of the present invention is disclosed in SEQ ID NO:38.

Another embodiment of a responding cell activation protein of the present invention includes a CD45 protein comprising an extracellular domain of an isoform of a CD45 protein. A CD45 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 556 of CD45 protein, in which the initiating Met is residue 1. For human CD45 coding sequence, see Streuli et al., 1987, *J.Exp. Med.* 166: 1548-1566; Genbank Y00638; and Swissprot P08575. According to the present invention, an isoform of a CD45 protein is any CD45 protein that is formed by the alternative splicing of exons A, B, and C of CD45; such isoforms are well known to those skilled in the art. CD45 isoforms of the present invention include an isoform in which none of the exons are spliced out, an isoform in which all of the exons are spliced out, an isoform in which any one of exons A, B, or C is spliced out, and an isoform in which any combination of exons A, B, and C are spliced out. A CD45 protein of the present invention more preferably comprises any isoform of the amino acid sequence disclosed in SEQ ID NO:13 and a leader sequence. A preferred leader sequence to be used

with a CD45 protein of the present invention is disclosed in SEQ ID NO:39.

Another embodiment of a responding cell activation protein of the present invention includes a CD48 protein having a pseudovariable and a pseudoconstant extracellular domains of CD48 protein. A CD48 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 220 of CD48 protein, in which the initiating Met is residue 1. For human CD48 coding sequence, see Killeen et al., 1988, *EMBO J.* 7: 3087-3091; Genbank X06341, M37766, M59904; and Swissprot P09326. A CD48 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:14 and a leader sequence. A preferred leader sequence to be used with a CD48 protein of the present invention is disclosed in SEQ ID NO:40.

Another embodiment of a responding cell activation protein of the present invention includes a B7.1 protein having a pseudovariable and a pseudoconstant extracellular domain of B7.1 protein. A B7.1 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 242 of B7.1 protein, in which the initiating Met is residue 1. For human B7.1 coding sequence, see Freeman et al., 1989, *J. Immunol.* 143: 2714-2722; Genbank M27533. A B7.1 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:15 and a leader

sequence. A preferred leader sequence to be used with a B7.1 protein of the present inventi n is disclosed in SEQ ID NO:41.

Another embodiment of a responding cell activation protein of the present invention includes a B7.2 protein having an extracellular domain of B7.2 protein. A B7.2 protein of the present invention preferably comprises the amino acid sequence extending from about residue 1 to about residue 74 of B7.2 protein, in which the initiating Met is residue 1. For human B7.2 coding sequence, see Kubota et al., 1990, *J. Immunol.* 145, 3924-3931; Genbank M55561. A B7.2 protein of the present invention more preferably comprises the amino acid sequence disclosed in SEQ ID NO:16 and a leader sequence. An acceptable leader sequence to be used with a B7.2 protein of the present invention is disclosed, for example, in SEQ ID NO:29.

It is within the scope of the present invention that an RCA protein can be a portion of CD8 comprising a peptide that is capable of binding to a MHC Class I molecule in such a manner that cytotoxic T cell activity is regulated.

According to the present invention, at least a portion of an RCA protein of the present invention can be linked to at least a portion of an immunoglobulin (Ig) molecule to form an RCA:Ig chimeric molecule. An RCA protein is preferably linked to an Ig molecule by a peptide bond, which refers to the covalent chemical interaction between two amino acids. A preferred portion of an Ig molecule to

link to an RCA protein includes the constant region of an immunoglobulin molecule. Suitable C_L and C_H regions for use with an RCA:Ig chimeric molecule of the present invention include κ, λ, μ, γ1, γ2, γ2a, γ2b, γ3, γ4, α, α1, α2, σ and ε constant regions, with human κ, λ, μ, γ1, γ2, γ3, γ4, α1, α2, σ and ε constant regions being more preferred and human IgG2a being even more preferred. Any constant region of any antibody is suitable for use with the present invention. A preferred portion of a constant region to use includes at least one amino acid that enables an RCA:Ig molecule to be di-sulfide bonded to an SCM molecule of the present invention.

In a preferred embodiment, an RCA:Ig chimeric molecule of the present invention comprises a CD4:Ig chimeric molecule having the amino acid sequence disclosed in SEQ ID NO:17 and a leader sequence. A preferred leader sequence to be used with a CD4:Ig protein of the present invention is disclosed in SEQ ID NO:29.

In another preferred embodiment, an RCA:Ig chimeric molecule of the present invention comprises a CD2:Ig chimeric molecule having the amino acid sequence disclosed in SEQ ID NO:18 and a leader sequence. A preferred leader sequence to be used with a CD2:Ig protein of the present invention is disclosed in SEQ ID NO:30.

In another preferred embodiment, an RCA:Ig molecule of the present invention comprises a CD28:Ig chimeric molecule having the amino acid sequence disclosed in SEQ ID NO:19

and a leader sequence. A preferred leader sequence to be used with a CD28:Ig protein of the present inventi n is disclosed in SEQ ID NO:31.

In another preferred embodiment, an RCA:Ig chimeric molecule of the present invention comprises a CTLA4:Ig molecule having the amino acid sequence disclosed in SEQ ID NO:20 and a leader sequence. A preferred leader sequence to be used with a CTLA4:Ig protein of the present invention is disclosed in SEQ ID NO:32.

In another preferred embodiment, an RCA:Ig chimeric molecule of the present invention comprises a fas-ligand:Ig chimeric molecule having the amino aid sequence disclosed in SEQ ID NO:21 and a leader sequence. An acceptable leader sequence to be used with a Fas-ligand:Ig protein of the present invention is disclosed, for example, in SEQ ID NO:29.

One embodiment of a stimulator cell marker (SCM) molecule of the present invention includes a molecule capable of targeting an RCA protein of the present invention to a desired cell. In particular, an SCM molecule of the present invention includes, but is not limited to an immunoglobulin molecule (an antibody), a growth factor or a tissue-specific antigen. A suitable antibody for use as an SCM molecule of the present invention binds to a protein on the surface of a stimulator cell of the present invention. A preferred antibody of the present invention binds to a protein on the surface of a

tissue graft cell or a cell involved in an aut immune response. A m re preferred antibody of the present invention binds t a major histoc mpatibility molecule (MHC), including Class I and Class II, or an organ-specific molecule, such as molecules expressed on the surface of kidney cells (e.g., sodium-potassium-chloride cotransporters; see Herbert et al., 1994, *Clin. Invest.* 72: 692-694), liver cells (e.g., asialoglycoprotein receptor; see Merwin et al., 1994, *Bioconjugate Chem.* 5: 612-620; bile acid receptors; see Krmaer et al., 1992; *J. Bio. Chem.* 267: 18598-18604; LMA surface target molecules; see Stemerowicz et al., 1990, *J.Clin. Lab. Immunol.* 32: 13-19); heart cells (e.g., heart specific auto-antibodies; see Neumann, et al., 1992, *J. Immunol.* 148: 3806-3813; Traystman et al., 1991, *Clin. Exp. Immunol.* 86: 291-298); pancreas cells or bone marrow cells (e.g., c-kit receptor; see Okayama et al., 1994, *J. Immunol. Meth.* 169: 153-161; Bridell et al., 1992, *Blood* 79: 3159-3167.

In a preferred embodiment, an antibody useful as an SCM molecule of the present invention includes the immunoglobulin molecules WFL4F12.3, WFL3C6.1, BB7.2, PA2.1, 2.28M1, MA2.1, GAP A3, A11.1M, 4D12, BB7.1, B27M1, ME1, BB7.6, MB40.2, MB40.2, B27M2, SFR8-B6, Genox 3.53, G2a.5 and SFR3-DR5 (each described in ATCC Catalogue of Cell Lines and Hybridomas, 7th Edition, 1992 American Type Culture Collection).

It is within the scope of the present invention that an antibody can include a full-length antibody, an Fab fragment, an $F(ab')_2$ fragment or an F_v fragment of an antibody. An Fab fragment comprises one arm of an immunoglobulin molecule containing a light chain (V_L region + C_L region) paired with the heavy chain variable region (V_H region) and a portion of a heavy chain constant region (C_H region) CH1 domain. An $F(ab')_2$ fragment corresponds to two di-sulfide bonded arms of an immunoglobulin molecule, each arm containing a L chain (V_L region + C_L region) paired with a V_H region and a CH1 domain. An F_V fragment refers to a portion of an immunoglobulin molecule V_L region paired with a V_H region. Thus, an antibody of the present invention can include the variable (V), diversity (D) and junction (J) regions, the V,D, J and CH1 regions or the full-length protein of any preferred antibody described herein.

A suitable growth factor for use as an SCM molecule of the present invention binds to a receptor on the surface of a stimulator cell of the present invention. A preferred growth factor of the present invention binds to a receptor on the surface of a tissue graft cell or a cell involved in an autoimmune response. A more preferred growth factor of the present invention includes, but is not limited to thyroid stimulating hormone (TSH), vasopressin or corticotropin.

A suitable growth factor for use as an SCM molecule of the present invention binds to a tissue-specific marker on

the surface of a stimulator cell of the present invention. A preferred SCM molecul of the present invention binds to a tissue specific marker on the surface of a tissue graft cell or a cell involved in an autoimmune response. A more preferred SCM molecule of the present invention includes, but is not limited to asialoglycoprotein receptor, (TSH) receptor, vasopressin receptor or corticotropin receptor.

According to the present invention, an RCA protein or an SCM molecule can comprise a derivative of an RCA protein or an SCM molecule. In accordance with the present invention, a "derivative" refers to any compound that is able to mimic the ability of a component of an RCA protein or an SCM molecule of the present invention. A derivative of an RCA protein or an SCM molecule can be an amino acid sequence that has been modified to decrease its susceptibility to degradation but that still retains binding activity. Other examples of derivatives include, but are not limited to, protein-based compounds, carbohydrate-based compounds, lipid-based compounds, nucleic acid-based compounds, natural organic compounds, synthetically derived organic compounds, anti-idiotypic antibodies and/or catalytic antibodies, or fragments thereof having desired T cell regulatory activity. A derivative can be obtained by, for example, screening libraries of natural and synthetic compounds for compounds capable of binding to a CD4 or CD2 co-receptor or an MHC antigen, as disclosed herein. A derivative of a CD4, CD2

or immunogl bulin molecule can also be obtained by, for example, rational drug design. In a rational drug design procedure, the three-dimensional structure of a compound of the present invention can be analyzed by, for example, nuclear magnetic resonance (NMR) or x-ray crystallography. The three-dimensional structure can then be used to predict structures of potential derivatives by, for example, computer modeling. The predicted derivative structures can then be produced by, for example, chemical synthesis, recombinant DNA technology, or by isolating a mimetope from a natural source (e.g., plants, animals, bacteria and fungi).

In particular, a derivative of an RCA protein or an SCM molecule can include amino acid substitution or insertion mutants into which an amino acid has been substituted or inserted, the amino acid being capable of forming a di-sulfide bond with another amino acid (e.g., a cysteine or a proline).

An RCA protein or an SCM molecule of the present invention can be soluble or membrane-bound. Amino acid sequences can be genetically engineered to create soluble forms by introducing a translational stop codon into the coding sequences of an RCA protein or an SCM molecule, upstream of the cytoplasmic domains and/or the hydrophobic transmembrane domains, using technologies known to those of skill in the art (e.g., site-directed mutagenesis or PCR modification). An example of a soluble CD4 molecule

includes SEQ ID NO:17. An example of a soluble CD2 molecule includes SEQ ID NO:18. The resulting truncated CD4- r CD2- encoding nucleic acid molecules can be operatively linked to an expression vector containing one or more transcription or translation control regions to form a recombinant molecule, and the recombinant molecules can be expressed in a host cell.

Amino acid sequences can be genetically engineered to create membrane-bound forms by linking, or retaining the linkage of, the amino acid sequences of an RCA protein or an SCM molecule to amino acid sequences for transmembrane domains and/or amino acid sequences for cytoplasmic domains. Preferably, a membrane-form of an RCA protein or an SCM molecule of the present invention is designed such that the molecule can be inserted into the plasma membrane of a cell and remain associated with the membrane over time. An embodiment of a plasma membrane-bound form of an RCA protein or an SCM molecule preferably comprises a full-length transmembrane domain and cytoplasmic domain of an RCA protein or an SCM molecule. Such membrane-bound forms can be produced by operatively linking nucleic acid molecules encoding full-length RCA protein or SCM molecule to an expression vector containing one or more transcription or translation control regions to form a recombinant molecule, and expressing the recombinant molecules in a host cell. Alternatively, an RCA protein or an SCM molecule can be designed such that the molecule can

be anchored in a lipid bilayer when incorp rated into lipid-containing substrates by being added ex genously. As used herein, the term "anch ring" refers to the insertion of a molecule in a lipid-containing substrate such that any extracellular domains are on the outside of the substrate.

In one embodiment, an RCA protein or an SCM molecule of the present invention is produced by culturing a cell transformed with a recombinant molecule comprising a nucleic acid molecule operatively linked to an expression vector, in which the nucleic acid molecule comprises a nucleic acid sequence encoding an RCA protein or an SCM molecule.

A recombinant molecule of the present invention comprises a nucleic acid molecule, encoding an RCA protein or an SCM molecule of the present invention, operatively linked to a vector capable of being expressed in a host cell. As used herein, "operatively linked" refers to insertion of a nucleic acid sequence into an expression vector in such a manner that the sequence is capable of being expressed when transformed into a host cell. As used herein, an "expression vector" is an RNA or DNA vector capable of transforming a host cell and effecting expression of an appropriate nucleic acid sequence, preferably replicating within the host cell. An expression vector can be either prokaryotic or eukaryotic, and typically is a virus or a plasmid.

Construction of desired expression vectors can be performed by methods known to those skilled in the art and expression can be in eukaryotic or prokaryotic systems. Procaryotic systems typically used are bacterial strains including, but not limited to various strains of *E. coli*, various strains of *bacilli* or various species of *Pseudomonas*. In prokaryotic systems, plasmids are used that contain replication sites and control sequences derived from a species suitable for use with a host cell. Control sequences can include, but are not limited to promoters, operators, enhancers, ribosome binding sites, and Shine-Dalgarno sequences. Expression systems useful in eukaryotic host cells comprise promoters derived from appropriate eukaryotic genes. Useful mammalian promoters include early and late promoters from SV40 or other viral promoters such as those derived from baculovirus, polyoma virus, adenovirus, bovine papilloma virus or avian sarcoma virus. Expression vectors of the present invention include any vectors that function (i.e., direct gene expression) in recombinant cells of the present invention including bacterial, yeast, other fungal, insect and mammalian cells. Preferred expression vectors of the present invention include vectors containing immunoglobulin H chain promoters and/or L chain promoters. In particular, an expression vector of the present invention includes a polyhedrin promotor for CD4 or CD2 for use in a baculovirus expression system or a CMV immediate early promotor or a RSV-LTR

promotor for use in a eukaryotic cell system. Useful mammalian enhancers include immunoglobulin H chain nhancers and/or L chain enhancers. Particularly preferred expression vectors for use with the present invention include baculovirus transfer vectors pVL1393, pAcUw51 or pAcAB3. In a preferred embodiment, an expression vector of the present invention comprises pVLCD2-IgG2a or pVLCD4-IgG2a.

An expression system can be constructed from any of the foregoing control elements operatively linked to the nucleic acid sequences of the present invention using methods known to those of skill in the art (see, for example, Sambrook et al., *ibid.*).

Host cells of the present invention can be cells naturally capable of producing an RCA protein or an SCM molecule, or cells that are capable of producing an RCA protein or an SCM molecule when transfected with a nucleic acid molecule encoding such molecules. Host cells of the present invention include, but are not limited to bacterial, fungal, insect and mammalian cells. Suitable host cells include mammalian cell, preferably a fibroblast, a pluripotent progenitor cell, an epithelial cell, a neural cell, a T cell line and a B cell line.

In one embodiment, a host cell is transformed with: (1) a first recombinant molecule comprising a nucleic acid molecule operatively linked to an expression vector, the nucleic acid molecule having a sequence encoding a first

protein including an RCA protein, particularly CD4, CD2, CD28, CTL4A, fas-ligand, CD5, CD7, CD9, CD11, CD18, CD27 , CD43, CD45, CD48, B7.1 and B7.2, and even more particularly CD4, CD2, CD28, CTL4A, fas-ligand; and (2) a second recombinant molecule comprising a nucleic acid molecule operatively linked to an expression vector, the nucleic acid molecule having a sequence encoding a second protein comprising a stimulatory cell marker molecule that differentiates a host cell from a tissue graft cell to form a recombinant cell.

Transformed recombinant cells of the present invention are cultured under conditions effective to produce such an RCA protein and SCM molecule. The protein and molecule can then be recovered from the culture medium and/or the cells. Effective conditions to produce an RCA or SCM molecule include, but are not limited to appropriate culture media, cell density, temperature, pH and oxygen conditions. One of skill in the art can choose appropriate culture conditions based on the type of cell being cultured and the amount of protein one desires to produce.

Depending on the expression vector used for production, resultant molecules can either remain within the recombinant cell, be retained on the outer surface of the recombinant cell, or be secreted into the culture medium. As used herein, the term "recovering" refers to collecting the culture medium containing the molecule

and/or recombinant cells. Recovery need not imply additional steps of separation or purification.

After recovery, an RCA protein or SCM molecule can be purified using a variety of standard protein purification techniques such as, but not limited to, size separation chromatography, reverse phase chromatography, chromatofocussing, hydroxyapatite adsorption and electrophoresis systems, affinity chromatography, ion exchange chromatography, ammonium sulfate precipitation, filtration, centrifugation, hydrophobic interaction chromatography, gel filtration chromatography, high pressure liquid chromatography and differential solubilization. Isolated proteins are preferably retrieved in substantially pure form. As used herein, "substantially pure" refers to a purity that allows for the effective use of the molecule as a heretofore described T cell veto molecule.

Soluble RCA proteins or SCM molecules of the present invention can be purified using, for example, immunoaffinity chromatography using an antibody capable of binding to CD4, CD2, CD28, CTL4A, fas-ligand or the C region of an immunoglobulin molecule or an antigen capable of binding to the V region of immunoglobulin molecule. RCA proteins or SCM molecules anchored in a lipid-containing substrate can be recovered by, for example, density gradient centrifugation techniques.

One aspect of the present invention is a method for producing a T cell veto molecule, comprising: (a) providing a first protein comprising an RCA protein, in particular CD4, CD2, CD28, CTL4A, fas-ligand protein, CD5 protein, CD7 protein, CD9 protein, CD11 protein, CD18 protein, CD27 protein, CD43 protein, CD45 protein, CD48 protein, B7.1 protein and B7.2 protein; (b) providing a second protein comprising an SCM molecule; and (c) linking the first protein to the second protein to form a chimeric molecule. As used herein, the term "linked" can refer to covalently attaching an RCA protein to an SCM molecule. A suitable reagent for the linking step includes any reagent capable of creating di-sulfide bonds between an RCA protein and an SCM molecule. Preferably, an RCA protein can be covalently associated to an SCM molecule by several methods including, for example, treatment with chemicals capable of linking di-sulfide bonds, glutaraldehyde linkage, photoaffinity labeling, treatment with carbodiimides and treatment with other cross-linking chemicals standard in the art. Preferably, an RCA protein can be covalently associated to an SCM molecule by treatment with chemicals capable of linking di-sulfide bonds, in particular using N-succinimidyl-3-1-(1-pyridyldthio)-propionate.

Following chemical cross-linking of an RCA protein to an SCM molecule, the resulting chimeric T cell veto molecules are recovered from those proteins that have not been linked using methods standard in the art. Preferably,

T cell veto molecules are recovered by size separation chromat graphy.

A T cell veto molecule of the present invention preferably comprises a CD4:Ig protein having the amino acid sequence represented by SEQ ID NO:17, di-sulfide bonded to an antibody that binds specifically to an MHC molecule, in particular 14-4-4 to form the CD4:14 T cell veto molecule (see Examples section). A T cell veto molecule of the present invention also preferably comprises a CD2:Ig having the amino acid sequence represented by SEQ ID NO:18, di-sulfide bonded to an antibody that binds specifically to an MHC molecule, in particular 14-4-4 to form the CD2:14 T cell veto molecule.

According to the present invention, different embodiments of a T cell veto molecule of the present invention can be combined to form a composition of the present invention. A preferred composition comprises a CD4 protein linked to a target molecule that differentiates a host cell from a tissue graft cell, a chimeric molecule having a CD2 protein linked to target molecule that differentiates a host cell from a tissue graft cell, a chimeric molecule having a CD28 protein linked to target molecule that differentiates a host cell from a tissue graft cell, a chimeric molecule having a CTL4A protein linked to target molecule that differentiates a host cell from a tissue graft cell, a chimeric molecule having a fas-ligand protein linked to target molecule that

differ ntiates a host cell from a tissue graft cell and mixtures thereof. A more preferred comp sition comprises CD4:14 T cell veto molecule, CD2:14 T cell veto molecule and mixtures thereof.

Another aspect of the present invention comprises formulating a T cell veto molecule of the present invention with a pharmacologically acceptable carrier to form a therapeutic composition of the present invention. As used herein, a "carrier" refers to any substance suitable as a vehicle for delivering a T cell veto molecule to a suitable *in vitro* or *in vivo* site of action. As such, carriers can act as an excipient for formulation of a therapeutic or experimental reagent containing a T cell veto molecule. Preferred carriers are capable of maintaining a T cell veto molecule in a form that is capable of binding to a stimulating cell and regulating the activity of a responding cell. Examples of such carriers include, but are not limited to water, phosphate buffered saline, saline, Ringer's solution, dextrose solution, serum-containing solutions, Hank's solution and other aqueous physiologically balanced solutions. Aqueous carriers can also contain suitable auxiliary substances required to approximate the physiological conditions of the recipient, for example, enhancement of chemical stability and isotonicity. Suitable auxiliary substances include, for example, sodium acetate, sodium chloride, sodium lactate, potassium chloride, calcium chloride, sorbitan

monolaurate, triethanolamine oleate, and other substances used to produce phosphate buffer, Tris buffer and bicarbonate buffer. Auxiliary substances can also include preservatives, such as thimerosal, m or o-cresol, formalin and benzyl alcohol. Preferred auxiliary substances for aerosol delivery include surfactant substances nontoxic to a recipient, for example, esters or partial esters of fatty acids containing from about 6 to about 22 carbon atoms. Examples of esters include, caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids. Therapeutic compositions of the present invention can be sterilized by conventional methods and/or lyophilized. Standard formulations can either be liquid injectables or solids which can be taken up in a suitable liquid as a suspension or solution for injection. Thus, in a non-liquid formulation, the excipient can comprise dextrose, human serum albumin, preservatives, etc., to which sterile water or saline can be added prior to administration.

A therapeutic composition can further comprise a T cell veto molecule combined with a compound capable of suppressing an immune response. Such regulatory compounds include, but are not limited to, immunosuppressive drugs or antibodies that specifically bind to interleukins.

Useful carriers for membrane-bound T cell veto molecules include any artificial or natural lipid-containing substrate, preferably cells, cellular

membranes, liposomes and micelles. Cellular carriers of the present invention include cells capable of producing a T cell veto molecule. Preferred cells are disclosed in detail herein.

Embodiments of the present invention comprise the use of a T cell veto molecule, as disclosed in the present invention, to suppress the activity of immune cells *in vivo* or *in vitro*. In particular, a T cell veto molecule of the present invention is useful for administration to subjects to immunosuppress subjects against, for example, autoantigens, allergens, engraftments and agents perfused into subjects (i.e., blood factors and platelets). This process is particularly applicable for purposes of specific immunosuppression, and derives from the novel structure of a T cell veto molecule of the present invention. Immune cells refers to cells typically involved in an immune response (e.g., T cells, APCs etc.). Immunosuppression refers to inhibiting an immune response by, for example, killing or anergizing (i.e., diminishing reactivity by a T cell to an antigenic peptide) particular cells involved in the immune response.

A particular advantage of a T cell veto molecule of the present invention is that such molecules can be designed to regulate the activity of one type of responder cell without regulating the activity of another type of responder cell. For example, a CD4:anti-class II MHC T cell veto molecule of the present invention can selectively

regulate the activity of CD4$^+$ T cells without regulating the activity of CD8$^+$ T cells. Similarly, a CD8:anti-class I MHC T cell veto molecule can selectively regulate the activity of CD8$^+$ T cells without regulating the activity of CD4$^+$ T cells.

Prior to the present invention, one theory of T cell veto suggested that simultaneous engagement of T cells through the T cell receptor and through the $\alpha 3$ domain of the class I MHC molecule results in the deletion of the T cell. If this theory is correct, then a veto molecule of the present invention which includes CD8, for example, could be targeted to a stimulator cell such that the stimulator cell effectively "expresses" the CD8. This stimulator cell would then have the capability to provide the above-mentioned deleterious trigger to an alloreactive T cell by virtue of its ability to simultaneously engage an alloreactive T cell receptor and the T cell's class I MHC. Furthermore, according to this theory of T cell veto, a CD8 veto molecule would be expected to provide the same deleterious trigger to either a CD8$^+$ or a CD4$^+$ T cell, since both T cell types express a T cell receptor and class I MHC. The present inventors have unexpectedly discovered, however, that such a CD8 veto molecule is in fact incapable of inhibiting CD4$^+$ T cells, and similarly, a veto molecule which includes CD4 inhibits CD4$^+$ T cells, but is incapable of inhibiting CD8$^+$ T cells (See Example 4 below). The present inventors describe for the first time herein T cell

vet molecules which can selectively inhibit one type of responder cell (e.g., a $CD4^+$ T cell) without inhibiting another type of responder cell (e.g., a $CD8^+$ T cell). The disclosure herein of T cell veto molecules which can inhibit different subsets of T cells in such a highly selective manner is significant, because different subsets of T cells have different functions in immune responses. In many disease states and conditions involving an immune response, it may be desirable to regulate the activity of one subset of T cell while leaving the activity of another subset of T cell intact. For example, it may be desirable to inhibit the activity of $CD4^+$ T cells at a particular site *in vivo* in a given autoimmune disease, but leave other immune functions (e.g., $CD8^+$ T cell function and all T cell functions at other *in vivo* sites) intact. In another situation, it may be desirable only to target activated T cells at a particular site. In this scenario, selective inhibition of T cells expressing Fas by using a veto molecule which includes Fas ligand may be desirable. The T cell veto molecules and methods disclosed herein provide such selective inhibition.

One aspect of the present invention is a method to suppress an immune response comprising: (a) providing a chimeric molecule having a protein, selected from the group consisting of CD4, CD2, CD28, CTL4A, fas-ligand, CD5 protein, CD7 protein, CD9 protein, CD11 protein, CD18 protein, CD27 protein, CD43 protein, CD45 protein, CD48

protein, B7.1 protein and B7.2 protein linked to a responding cell marker molecule; and (b) exposing the chimeric molecule to an antigen presenting cell that can respond to the chimeric molecule, for a time and under conditions sufficient to reduce a cellular immune response of a T lymphocyte to an antigen. The present method is particularly useful for reducing the response of a T cell to an antigen comprising an alloantigen or a processed antigen.

Preferably, the chimeric molecule is contacted with the antigen presenting cell *in vivo*. Acceptable protocols to administer therapeutic compositions *in vivo* in an effective manner include individual dose size, number of doses, frequency of dose administration and mode of administration. Determination of such protocols can be accomplished by those skilled in the art depending upon a variety of variables, including the animal to be treated, the type of treatment being administered (e.g., graft rejection prevention or treatment of an autoimmune disease) and the stage of disease.

Effective doses to immunosuppress an animal include doses administered over time that are capable of alleviating an immune response by the animal. For example, a single suppressing dose can comprise an amount of a therapeutic composition of the present invention that sufficiently ablates an immune response against an alloantigen, compared with an immune response in the

absence of the therapeutic compositi n. Alternatively, a single suppressing dose can comprise an amount of a therapeutic composition of the present invention that partially reduces an immune response against an alloantigen, compared with an immune response in the absence of the therapeutic composition. In this case, repeated administrations of the single dose could be given to an animal until the immune response is sufficiently ablated. A suitable single dose of a therapeutic composition of the present invention is a dose that is capable of substantially inhibiting a T cell response to an antigen when administered one or more times over a suitable time period. A single dose of a therapeutic composition preferably ranges from about 1 micrograms (μg) to about 100 milligrams (mg), more preferably ranges from about 10 μg to about 10 mg and even more preferably ranges being from about 100 μg to about 1 mg of a therapeutic composition per subject, of a toleragenic therapeutic reagent per subject. Effective doses to suppress an animal include doses administered over time that are capable of decreasing T cell activation to an antigen by an animal. For example, a first suppressing dose can comprise an amount of a therapeutic composition of the present invention that prevents an immune response when administered to an animal. A second suppressing dose can comprise a lesser amount of the same therapeutic composition than the first dose to continue prevention of an immune response. For example, if

a first dose can comprise about 10^6 arbitrary units of a TLV molecule, then a second dose can comprise about 10^3 arbitrary units of a TLV molecule. Effective suppressing doses can comprise decreasing concentrations of a therapeutic composition of the present invention necessary to maintain an animal in a suppressed state, such that the animal does not have an immune response to subsequent exposure to an antigen.

The manner of administration of a therapeutic composition of the present invention can depend upon the particular purpose for the delivery (e.g., treatment of disease or prevention of graft rejection), the overall health and condition of the recipient and the judgement of the physician or technician administering the therapeutic composition. A therapeutic composition of the present invention can be administered to an animal using a variety of methods. Such delivery methods can include parenteral, topical, oral or local administration, such as intradermally or by aerosol. A therapeutic composition can be administered in a variety of unit dosage forms depending upon the method of administration. For example, unit dosage forms suitable for oral administration to the intestinal region of an animal include powder, tablets, pills and capsules. Preferred delivery methods for a therapeutic composition of the present invention include intravenous administration and local administration by, for example, injection or topical administration. For

particular modes of delivery, a therapeutic composition of the present invention can be formulated in an excipient of the present invention. A therapeutic reagent of the present invention can be administered to any animal, preferably to mammals, and more preferably to humans.

As an example of a T cell veto molecule-mediated immunosuppressive therapeutic process, the sequence of steps that can be executed for inducing suppression in a prospective transplant recipient for the allogeneic MHC molecule of the transplant donor, in order to prevent immunological rejection of the graft following transplantation, are as follows:

(a) gene constructs are assembled for producing human CD4, human CD2 and specific antibodies that bind to MHC Class II molecules. In each case, the coding sequence for the extracellular domain of CD4 or CD2 is subcloned into pVL1393 vector.

(b) The subcloned coding sequences are transfected into insect cells in order to produce recombinant CD4, CD2 and immunoglobulin protein. The transfected cells are maintained in serum-free, protein-free medium.

(c) Dimers of soluble human CD4 or human CD2 are harvested from the cell cultures by the following method. Tissue culture supernatant, adjusted to pH 8.5, is filtered through a Mono-Q-Sepharose column (Pharmacia, Uppsala, Sweden). The flow-though is loaded onto a Wheatgerm-Lectin-Sepharose column (Pharmacia), and CD4 or CD2 are

eluted with 5% N-ac tyl-glucosamine. The eluate is dialyzed against 20 mM $NaC_2H_3O_2$ (pH 5.4, Sigma), concentrated and l aded onto Mono-S-Sepharose (Pharmacia) pre-equilibrated with 20 mM HEPES (pH 8.0, Sigma). Soluble CD4 or CD2 is eluted as the first peak of a NaCl-gradient (20 mM to 500 mM, Sigma) in 20 mM HEPES (pH 8.0) and dialyzed against PBS. The purity of the CD4 or CD2 dimers is analyzed by resolution using SDS-PAGE gel electrophoresis. Immunoglobulin molecules are purified from tissue-culture supernatant on a Protein A-Sepharose column (Pharmacia) using a standard protocol.

(d) Soluble CD4 or CD2, and immunoglobulin are cross-linked using the heterobifunctional cross-linker, N-succinimidyl-3-(1-pyridyldithio)-propionate (SPDP, Pharmacia) according to standard methods, at pH 7.4. Cross-linked proteins are purified from unreacted proteins and SPDP by passage of the preparation over on a Sephadex G25 column (Pharmacia).

(e) A subject who is to undergo a transplant is assessed for alloreactivity to donor allo-MHC by isolating peripheral blood mononuclear cells (PBMC) from the prospective transplant recipient's blood, and setting up a mixed lymphocyte reaction (MLR) with the recipient's PBMC as responders and irradiated (1500 rads) donor PBMC as stimulators. If a significant proliferative response is noted, a therapeutic composition comprising a TLV molecule or composition thereof, corresponding to the donor

allo-MHC, are infused intravenously int th graft recipi nt about 4 to about 1 weeks prior to the planned transplantation procedure.

(f) At about 2 to about 1 weeks prior to the transplantation date, the MLR is repeated, and if a residual proliferative response between recipient responders and donor stimulators persists, the therapeutic composition is reinfused into the graft recipient.

(g) The MLR is repeated post-transplantation to assess the need for booster doses to the graft recipient of a therapeutic composition which can be administered systemically or topically, as required.

Another example of a TLV molecule-mediated immunosuppressive therapeutic process, the sequence of steps (a) through (d) from the foregoing example are repeated and the cells of a graft are coated with a therapeutic composition of the present invention, and then the graft is transplanted into a recipient. The process is applicable to a variety of graft types, including vascularized solid tissue (e.g., kidney, heart, liver, lung and skin) and dispersed cellular populations (e.g., bone marrow cells). Treatment of a solid graft can comprise the steps of: (1) perfusing the donor organ at the time of surgery and prior to its resection, with about 100 μg/ml of a therapeutic composition comprising TLV molecules contained in normal saline via a bolus injection into a vessel entering the organ; and (2) catherizing the vessel,

resecting the organ and storing the organ in a solution supplemented with a therapeutic composition of the present invention until transplantation. Treatment of a dispersed cell population can comprise the steps of: (1) aspirating a cell population from a donor and separating the cells from undesired blood elements using methods standard in the art; and (2) resuspending the isolated donor cells in about 10 μg/ml of a therapeutic composition comprising TLV molecules contained in normal saline for about 2 hours at 5° C until transplantation.

It is within the scope of the invention that the pre-treatment of a recipient and the treatment of a graft tissue can be performed separately or in combination, depending on the parameters of the transplantation (e.g., donor-recipient allotype match, type of tissue etc.). It is also within the scope of the present invention that modifications can be made to the therapeutic processes disclosed herein. For example, subjects afflicted with autoimmune disease can treated by systemically administering a therapeutic composition of the present invention using similar steps as those outlined for the pre-treatment of graft recipients. Alternatively, a therapeutic composition can be administered to subjects afflicted with localized autoimmune diseases, such as rheumatoid arthritis, by directly injecting the composition into a diseased area such as a joint. Other examples of autoimmune diseases that can be treated using a therapeutic

composition of the present invention include systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, insulin-dependent diabetes mellitus, multiple sclerosis, celiac disease, autoimmune thyroiditis, Addison's disease, Graves' disease and rheumatic carditis.

One embodiment of a therapeutic method of the present invention includes administering a high dose of corticosteroids, for example dexamethasone in two injections (about 1mg per day for two days, followed by the step of administering a T cell veto molecule of the present invention for the next four weeks, at a concentration of about 1mg per injection (intravenous) twice a week.

The following experimental results are provided for purposes of illustration and are not intended to limit the scope of the invention.

EXAMPLES

Example 1

This example describes the production of chimeric cDNA clones encoding CD2:Ig or CD4:Ig molecules.

A. Production of Human Blood or 15.5.5. cDNA

Two separate samples of cDNA were prepared using mRNA isolated from human blood or 15.5.5 cells (described in Ozato et al., 1980, *J. Immunol.* 124: 533) by the following method. About 2mL Trizol (Gibco-BRL, Gaithersburg, MD) was added to the cells. The cells were then extracted 1 time with 100% chloroform. The RNA in the aqueous phase was

treated with 100% is propyl alcohol and the resulting precipitate was pelleted at 12,000 x rpm for 10 minutes. The resulting pellet containing RNA was resuspended in water containing 0.1% diethylpyrocarbonate (DEPC).

The RNA was then reverse transcribed into cDNA according to methods standard in the art using reverse transcriptase, oligo dT as a primer and a mixture of nucleotides.

B. Production of CD2, CD4 and Immunoglobulin cDNA

cDNA encoding the extracellular domains of CD2 was produced by polymerase chain reaction (PCR) amplification using the following method. Human cDNA described in Section A was combined with CD2 sense primer (5' CGC TCT AGA ATG AGC TTT CCA TGT AAA TTT GTA 3'; SEQ ID NO:22) and CD2 anti-sense primer (5' TGT GGG CCC TCT GGG CTC GTC CAG ACC TTT CTC TGG 3'; SEQ ID NO:23). The mixture was amplified for 3 cycles at 94°C (60 sec.), 50°C (30 sec.), 72°C (60 sec.) followed by 27 cycles at 94°C (60 sec.), 55°C (30 sec.), and 72°C (60 sec.). A 10 minute 72°C final elongation was then performed to produce amplified CD2 cDNA.

cDNA encoding the two amino terminal domains of CD4 was produced by PCR amplification using the following method. Human cDNA described in Section A was combined with CD4 sense primer (5' CGC TCT AGA ATG AAC CGG GGA GTC CCT 3'; SEQ ID NO:24) and CD4 anti-sense primer (5' GGG CCC TCT GGG CTC AGC TAG CAC CAC GAT GTC T 3'; SEQ ID NO:25).

The mixture was then amplified as described above to produce amplified CD4 cDNA.

cDNA encoding the Fc d main of the 15.5.5 anti-class I (IgG2a isotype) monoclonal antibody was produced as follows. The cDNA produced from the 15.5.5 cell cDNA described in Section A was mixed with either a first IgG2a sense primer(CD2 sense primer: 5' CCA GAG AAA GGT CTG GAC GAG CCC AGA GGG CCC AC 3'; SEQ ID NO:26) or a second IgG2a sense primer (CD4 sense primer: 5' AGA CAT CGT GGT GCT AGC TGA GCC CAG AGG GCC C 3'; SEQ ID NO:27), and IgG2a anti-sense primer (5' GGC GAA TTC TTT ACC CGG AGT CCG GGA GAA GCT 3'; SEQ ID NO:28). The cDNAs were amplified using the conditions described in above to produce a first and a second IgG2a Fc domain cDNA.

C. Production of Chimeric Molecules

PCR amplification was then used to link cDNA encoding the extracellular domains of CD2 or CD4 to cDNA encoding the Fc domain of the 15.5.5 anti-class I monoclonal antibody (I.e., CD2-IgG2a fusion cDNA and CD4-IgG2a fusion cDNA).

CD2-IgG2a fusion cDNA was produced by combining cDNA encoding the extracellular domains of CD2 with cDNA encoding the Fc domain of 15.5.5 antibody produced using the CD2 sense primer. CD4-IgG2a fusion cDNA was produced by combining cDNA encoding the amino terminal domains of CD4 with cDNA encoding the Fc domain of 15.5.5 antibody produced using the CD4 sense primer. Both of the foregoing

mixtures were amplified using the amplification conditions described in s cti n B.

Example 2

This example describes the production of expression vectors encoding chimeric CD2:IgG2a or CD4:IgG2a fusion molecules.

Each of the CD2:IgG2a or CD4:IgG2a fusion cDNA described in Example 1 were purified on a 1.0% agarose gel and recovered by Geneclean Kit (BIO 101 Inc., LaJolla, CA). The gel purified CD2:IgG2a fragment was directly ligated into PCRII vector (Invitrogen, San Diego, CA). The CD4:IgG2a fragment was also directly ligated into the PCRII vector. The PCRII vector is a linear vector with poly T overhangs for direct ligation.

InvaF' E. Coli (obtained from Invitrogen) were then transformed with either pCD2:IgG2a or pCD4:IgG2a and the colonies were grown on LB plates containing about 100mg/mL ampicillin. Resulting colonies were screened by PCR amplification using appropriate primers.

pCD2:IgG2a or pCD4:IgG2a plasmid was then isolated from bacterial colonies by propagating in liquid culture comprising LB broth and 50mg/mL ampicillin and purifying the plasmid using methods standard in the art (see Sambrook et al., *ibid.*). Purified plasmid DNA was then digested with XbaI and EcoRI to yield a fragment of cDNA encoding a CD2-IgG2a fusion molecule or cDNA encoding a CD4-IgG2a fusion molecule. These fragments were then gel-purified as

described above and separately ligated into the baculovirus transfer vector PVL 1393 (obtained from Pharmingen, San Diego, CA) which had previously been digested with XbaI and EcoRI, to form the expression vectors pVLCD2:IgG2a or pVLCD4:IgG2a. The expression vectors were then transformed into InvaF' E. Coli, selected as described above and frozen at -70°C for later use.

Example 3

This Example shows that a CD4:anti-H-2^d, T lymphocyte veto molecule of the present invention, which is targeted to the class II MHC of allogeneic stimulator cells in a T cell proliferation assay, demonstrates significant and specific inhibition of $CD4^+$ T-cell responses.

A transfectant secreting a soluble form of CD4 was obtained from K. Karjalainen (Basel Institute for Immunology). This material was purified by affinity chromatography and chemically (SPDP) cross-linked to the monoclonal antibody 14-4-4 which binds to certain class II MHC molecules (anti-H-2^d, but not anti-H-2^b) to form a hybrid antibody T lymphocyte veto molecule of the present invention.

Lymph node cells (50 or 200 x 10^5 per culture), which were enriched for CD4+ T-cells by two-step panning (purity >90% $CD4^+$ T-cells), were challenged with irradiated stimulator cells (200 x 10^5) in triplicate cultures (Figure 1). These mixed lymphocyte cultures (MLCs) were set up in

two combinations, C57BL/6 anti-BALB/c, where C57BL/6 cells are responders and BALB/c cells are stimulators (Figure 1A and 1B); and BALB/c anti-C57BL/6, where BALB/c cells are responders and C57BL/6 cells are stimulators (Figure 1C and 1D). Whereas in the first set of MLCs the hybrid antibody can bind to the stimulator cells (BALB/c H-2^d), in the second set it will not bind to the stimulator cells (C57BL/6 H-2^b), but will bind instead to the responder cells (BALB/c). Either the hybrid antibody, its non-linked components or medium only (nothing) was added to the MLCs. After 3 days, the cultures were pulsed with [^{3}H]-thymidine for 18 hours and then harvested.

Inhibition of proliferation was only observed when the hybrid antibody bound to the stimulators (Figure 1A and 1B), but not when the antibody bound to the responders (Figure 1C and 1D). In addition, supplementing cultures with non-linked components of the hybrid antibody, soluble CD4 and 14-4-4, did not result in any reduction of the response. Therefore, in order to inhibit proliferation of allo-reactive CD4$^+$ T-cells, the CD4 molecule has to be linked to 14-4-4 in a hybrid antibody and the hybrid antibody has to bind to the stimulator cells. Thus, hybrid antibody-mediated 'veto' is effective and specific.

To determine whether other T-cell functions besides proliferation were affected,. MLCs (C57BL/6 anti-BALB/c) were set up with CD4$^+$ T-cells. C57BL/6 CD4+ T-cell responders (200 x 10^5 per culture) were challenged with

irradiated BALB/c stimulator cells (200 x 10^5 per culture). Either the hybrid antib dy (shown in Figure 2 as) or its non-linked components (sh wn in Figure 2 as o) were added. After 3 days supernatants were harvested and tested for the presence of IL-2 and IL-4 by adding the supernatants to HT-2 cells in different dilutions [neat (1), 30% (0.3), 10% (0.1) and 3% (0.3)]. After 18 hours HT-2 cells were pulsed with [3H]-thymidine. As shown in a representative experiment (Figure 2), only the hybrid antibody was able to cause inhibition of IL-2/IL-4 production; its non-linked components failed to do so.

The foregoing experiment establishes the feasibility of this hybrid antibody inhibition by showing that 'veto' can be adapted for the inhibition of class II-reactive T-cells.

Example 4

The following example demonstrates that the activation of $CD4^+$ and $CD8^+$ T cells with a specificity for given stimulator cells (e.g., alloreactive T cells) can be inhibited in a highly selective manner.

In this experiment, a CD8:Ig hybrid molecule which included a CD8 α chain molecule and an anti-H-$2D^d$ antibody (anti-Class I MHC) was produced in a similar manner as described in Examples 1 and 2 for the CD4:Ig and CD2:Ig veto molecules. When this veto molecule was added to MLCs as described above, the veto molecule completely suppressed the lytic responses of $CD8^+$ T cells. Unexpectedly, the

CD8:anti-H-2^d veto molecule was incapable of inhibiting the action of $CD4^+$ T lymphocytes (data not shown). In a parallel experiment, when the CD4:anti-H-2^d veto molecule described in Example 3 above was added to the same cells, this CD4 veto molecule inhibited $CD4^+$ T cell activation, but was incapable of interfering with the development of $CD8^+$ cytotoxic effector T cells (data not shown). Therefore, these companion experiments demonstrated that targeted expression of CD8 on stimulator cells specifically inhibited $CD8^+$ T cells without interfering with the function of $CD4^+$ T cells, whereas targeted expression of CD4 on stimulator cells specifically inhibited $CD4^+$ T cells without interfering with the function of $CD8^+$ T cells.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Staerz, Uwe

(ii) TITLE OF INVENTION: NOVEL PRODUCT AND PROCESS FOR T LYMPHOCYTE VETO

(iii) NUMBER OF SEQUENCES: 41

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Sheridan Ross & McIntosh
(B) STREET: 1700 Lincoln Street, 35th Floor
(C) CITY: Denver
(D) STATE: Colorado
(E) COUNTRY: U.S.
(F) ZIP: 80203

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Connell, Gary J.
(B) REGISTRATION NUMBER: 32,020
(C) REFERENCE/DOCKET NUMBER: 2879-36

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (303) 863-9700
(B) TELEFAX: (303) 863-0223

(2) INFORMATI N FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 138 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Asn Lys Val Val Leu Gly Lys Lys Gly Asp Thr Val Glu Leu Thr Cys
1 5 10 15

Thr Ala Ser Gln Lys Lys Ser Ile Gln Phe His Trp Lys Asn Ser Asn
20 25 30

Gln Ile Lys Ile Leu Gly Asn Gln Gly Ser Phe Leu Thr Lys Gly Pro
35 40 45

Ser Lys Leu Asn Asp Arg Ala Asp Ser Arg Arg Ser Leu Trp Asp Gln
50 55 60

Gly Asn Phe Pro Leu Ile Ile Lys Asn Leu Lys Ile Glu Asp Ser Asp
65 70 75 80

Thr Tyr Ile Cys Glu Val Glu Asp Gln Lys Glu Glu Val Gln Leu Leu
85 90 95

Val Phe Gly Leu Thr Ala Asn Ser Asp Thr His Leu Leu Gln Gly Gln
100 105 110

Ser Leu Thr Leu Thr Leu Glu Ser Pro Pro Gly Ser Ser Pro Ser Val
115 120 125

Gln Cys Arg Ser Pro Arg Gly Lys Asn Ile
130 135

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 184 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys Glu Ile Thr Asn Ala Leu Glu Thr Trp Gly Ala Leu Gly Gln Asp
1 5 10 15

Ile Asn Leu Asp Ile Pro Ser Phe Gln Met Ser Asp Asp Ile Asp Asp
20 25 30

Ile Lys Trp Glu Lys Thr Ser Asp Lys Lys Lys Ile Ala Gln Phe Arg
35 40 45

Lys Glu Lys Glu Thr Phe Lys Glu Lys Asp Thr Tyr Lys L u Phe Lys
50 55 60

Asn Gly Thr Leu Lys Ile Lys His Leu Lys Thr Asp Asp Gln Asp Ile
65 70 75 80

Tyr Lys Val Ser Ile Tyr Asp Thr Lys Gly Lys Asn Val Leu Glu Lys
85 90 95

Ile Phe Asp Leu Lys Ile Gln Glu Arg Val Ser Lys Pro Lys Ile Ser
100 105 110

Trp Thr Cys Ile Asn Thr Thr Leu Thr Cys Glu Val Met Asn Gly Thr
115 120 125

Asp Pro Glu Leu Asn Leu Tyr Gln Asp Gly Lys His Leu Lys Leu Ser
130 135 140

Gln Arg Val Ile Thr His Lys Trp Ile Thr Ser Leu Ser Ala Lys Phe
145 150 155 160

Lys Cys Thr Ala Gly Asn Lys Val Ser Lys Glu Ser Ser Val Glu Pro
165 170 175

Val Ser Cys Pro Glu Lys Gly Leu
180

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 134 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr Asp Asn
1 5 10 15

Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser Arg Glu
20 25 30

Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu Val Cys
35 40 45

Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser Lys Thr
50 55 60

Gly Phe Asn Cys Asp ly Lys Leu Gly Asn lu Ser Val Thr Phe Tyr
65 70 75 80

Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys Lys Ile
85 90 95

Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly
100 105 110

Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe
115 120 125

Pro Gly Pro Ser Lys Pro
130

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 124 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15

Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30

Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45

Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60

Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80

Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95

Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Ala Gln Ile
100 105 110

Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp
115 120

(2) INFORMATI N FOR SEQ ID N :5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 145 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Pro Pro Glu Lys Lys Glu Leu Arg Lys Val Ala His Leu Thr Gly Lys
1 5 10 15

Ser Asn Ser Arg Ser Met Pro Leu Glu Trp Glu Asp Thr Tyr Gly Ile
20 25 30

Val Leu Leu Ser Gly Val Lys Tyr Lys Lys Gly Gly Leu Val Ile Asn
35 40 45

Glu Thr Gly Leu Tyr Phe Val Tyr Ser Lys Val Tyr Phe Arg Gly Gln
50 55 60

Ser Cys Asn Asn Leu Pro Leu Ser His Lys Val Tyr Met Arg Asn Ser
65 70 75 80

Lys Tyr Pro Gln Asp Leu Val Met Met Glu Gly Lys Met Met Ser Tyr
85 90 95

Cys Thr Thr Gly Gln Met Trp Ala Arg Ser Ser Tyr Lys Gly Ala Val
100 105 110

Phe Asn Leu Thr Ser Ala Asp His Leu Tyr Val Asn Val Ser Glu Leu
115 120 125

Ser Leu Val Asn Phe Glu Glu Ser Gln Thr Phe Phe Gly Leu Tyr Lys
130 135 140

Leu
145

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 349 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Arg Leu Ser Trp Tyr Asp Pro Asp Phe Gln Ala Arg Leu Thr Arg Ser
1 5 10 15

Asn Ser Lys Cys Gln Gly Gln Leu Glu Val Tyr Leu Lys Asp Gly Trp
20 25 30

His Met Val Cys Ser Gln Ser Trp Gly Arg Ser Ser Lys Gln Trp Glu
35 40 45

Asp Pro Ser Gln Ala Ser Lys Val Cys Gln Arg Leu Asn Cys Gly Val
50 55 60

Pro Leu Ser Leu Gly Pro Phe Leu Val Thr Tyr Thr Pro Gln Ser Ser
65 70 75 80

Ile Ile Cys Tyr Gly Gln Leu Gly Ser Phe Ser Asn Cys Ser His Ser
85 90 95

Arg Asn Asp Met Cys His Ser Leu Gly Leu Thr Cys Leu Glu Pro Gln
100 105 110

Lys Thr Thr Pro Pro Thr Thr Ile Ile Pro Pro Pro Thr Thr Thr Pro
115 120 125

Glu Pro Thr Ala Pro Pro Arg Leu Gln Leu Val Ala Gln Ser Gly Gly
130 135 140

Gln His Cys Ala Gly Val Val Glu Phe Tyr Ser Gly Ser Leu Gly Gly
145 150 155 160

Thr Ile Ser Tyr Glu Ala Gln Asp Lys Thr Gln Asp Leu Glu Asn Phe
165 170 175

Leu Cys Asn Asn Leu Gln Cys Gly Ser Phe Leu Lys His Leu Pro Glu
180 185 190

Thr Glu Ala Gly Arg Ala Gln Asp Pro Gly Glu Pro Arg Glu His Gln
195 200 205

Pro Leu Pro Ile Gln Trp Lys Ile Gln Asn Ser Ser Cys Thr Ser Leu
210 215 220

Glu His Cys Phe Arg Lys Ile Lys Pro Gln Lys Ser Gly Arg Val Leu
225 230 235 240

Ala Leu Leu Cys Ser Gly Phe Gln Pro Lys Val Gln Ser Arg Leu Val
245 250 255

Gly Gly Ser Ser Ile Cys Glu Gly Thr Val Glu Val Arg Gln Gly Ala
260 265 270

Gln Trp Ala Ala Leu Cys Asp Ser Ser Ser Ala Arg Ser Ser Leu Arg
275 280 285

Trp Glu Glu Val Cys Arg Glu Gln Gln Cys Gly Ser Val Asn Ser Tyr
290 295 300

Arg Val Leu Asp Ala Gly Asp Pro Thr Ser Arg Gly Leu Phe Cys Pro
305 310 315 320

His Gln Lys Leu Ser Gln Cys His Glu Leu Trp Glu Arg Asn Ser Tyr
325 330 335

Cys Lys Lys Val Phe Val Thr Cys Gln Asp Pro Asn Pro
340 345

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 154 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ala Gln Glu Val Gln Gln Ser Pro His Cys Thr Thr Val Pro Gly Ala
1 5 10 15

Ser Val Asn Ile Thr Cys Ser Thr Ser Gly Gly Leu Arg Gly Ile Tyr
20 25 30

Leu Pro Gln Leu Gly Pro Gln Pro Gln Asp Ile Ile Tyr Tyr Glu Asp
35 40 45

Gly Val Val Pro Thr Thr Asp Arg Arg Phe Arg Gly Arg Ile Asp Phe
50 55 60

Ser Gly Ser Gln Asp Asn Leu Thr Ile Thr Met His Arg Leu Gln Leu
65 70 75 80

Ser Asp Thr Gly Thr Tyr Thr Cys Gln Ala Ile Thr Glu Val Asn Val
85 90 95

Tyr Gly Ser Gly Thr Leu Val Leu Val Thr Glu Glu Gln Ser Gln Gly
100 105 110

Trp His Arg Cys Ser Asp Ala Pro Pro Arg Ala Ser Ala Leu Pro Ala
115 120 125

Pro Pro Thr Gly Ser Ala Leu Pro Asp Pro Gln Thr Ala Ser Ala Leu
130 135 140

Pro Asp Pro Pro Ala Ala Ser Ala Leu Pro
145 150

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

His Lys Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr
1 5 10 15

Tyr Asn Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys
20 25 30

Ala Ile His Tyr Ala Leu Asn Cys Cys Gly Leu Ala Gly Gly Val Ala
35 40 45

Gln Phe Ile Ser Asp Ile Cys Pro Lys Lys Asp Val Leu Glu Thr Phe
50 55 60

Thr Val Lys Ser Cys Pro Asp Ile Lys Glu Val Phe Asp Asn Lys
65 70 75

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1065 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Tyr Asn Leu Asp Val Arg Gly Ala Arg Ser Phe Ser Pro Pro Arg Ala
1 5 10 15

Gly Arg His Phe Gly Tyr Arg Val Leu Gln Val Gly Asn Gly Val Ile
20 25 30

Val Gly Ala Pro Gly Glu Gly Asn Ser Thr Gly Ser Leu Tyr Gln Cys
35 40 45

Gln Ser Gly Thr Gly His Cys Leu Pro Val Thr Leu Arg Gly Ser Asn
50 55 60

Tyr Thr Ser Lys Tyr Leu Gly Met Thr Leu Ala Thr Asp Pro Thr Asp
65 70 75 80

Gly Ser Ile Leu Ala Cys Asp Pro Gly Leu Ser Arg Thr Cys Asp Gln
85 90 95

Asn Thr Tyr Leu Ser Gly Leu Cys Tyr Leu Phe Arg Gln Asn Leu Gln
100 105 110

Gly Pro Met Leu Gln Gly Arg Pro Gly Phe Gln Glu Cys Ile Lys Gly
115 120 125

Asn Val Asp Leu Val Phe Leu Phe Asp Gly Ser Met Ser Leu Gln Pro
130 135 140

Asp Glu Phe Gln Lys Ile Leu Asp Phe Met Lys Asp Val Met Lys Lys
145 150 155 160

Leu Ser Asn Thr Ser Tyr Gln Phe Ala Ala Val Gln Phe Ser Thr Ser
165 170 175

Tyr Lys Thr Glu Phe Asp Phe Ser Asp Tyr Val Lys Trp Lys Asp Pro
180 185 190

Asp Ala Leu Leu Lys His Val Lys His Met Leu Leu Leu Thr Asn Thr
195 200 205

Phe Gly Ala Ile Asn Tyr Val Ala Thr Glu Val Phe Arg Glu Glu Leu
210 215 220

Gly Ala Arg Pro Asp Ala Thr Lys Val Leu Ile Ile Ile Thr Asp Gly
225 230 235 240

Glu Ala Thr Asp Ser Gly Asn Ile Asp Ala Ala Lys Asp Ile Ile Arg
245 250 255

Tyr Ile Ile Gly Ile Gly Lys His Phe Gln Thr Lys Glu Ser Gln Glu
260 265 270

Thr Leu His Lys Phe Ala Ser Lys Pro Ala Ser Glu Phe Val Lys Ile
275 280 285

Leu Asp Thr Phe Glu Lys Leu Lys Asp Leu Phe Thr Glu Leu Gln Lys
290 295 300

Lys Ile Tyr Val Ile Glu Gly Thr Ser Lys Gln Asp Leu Thr Ser Phe
305 310 315 320

Asn Met Glu Leu Ser Ser Ser Gly Ile Ser Ala Asp Leu Ser Arg Gly
325 330 335

His Ala Val Val Gly Ala Val Gly Ala Lys Asp Trp Ala Gly Gly Phe
340 345 350

Leu Asp Leu Lys Ala Asp Leu Gln Asp Asp Thr Phe Ile Gly Asn Glu
355 360 365

Pro Leu Thr Pro Glu Val Arg Ala Gly Tyr Leu Gly Tyr Thr Val Thr
370 375 380

Trp Leu Pro Ser Arg Gln Lys Thr Ser Leu Leu Ala Ser Gly Ala Pro
385 390 395 400

Arg Tyr Gln His Met Gly Arg Val Leu Leu Phe Gln Glu Pro Gln Gly
405 410 415

Gly Gly His Trp Ser Gln Val Gln Thr Ile His Gly Thr Gln Ile Gly
420 425 430

Ser Tyr Phe Gly Gly Glu Leu Cys Gly Val Asp Val Asp Gln Asp Gly
435 440 445

Glu Thr Glu Leu Leu Leu Leu Ile Gly Ala Pro Leu Phe Tyr Gly Glu
450 455 460

Gln Arg Gly Gly Arg Val Phe Ile Tyr Gln Arg Arg Gln Leu Gly Phe
465 470 475 480

Glu Glu Val Ser Glu Leu Gln Gly Asp Pro Gly Tyr Pro Leu Gly Arg
485 490 495

Phe Gly Glu Ala Ile Thr Ala Leu Thr Asp Ile Asn Gly Asp Gly Leu
500 505 510

Val Asp Val Ala Val Gly Ala Pro Leu Glu Glu Gln Gly Ala Val Tyr
515 520 525

Ile Phe Asn Gly Arg His Gly Gly Leu Ser Pro Gln Pro Ser Gln Arg
530 535 540

Ile Glu Gly Thr Gln Val Leu Ser Gly Ile Gln Trp Phe Gly Arg Ser
545 550 555 560

Ile His Gly Val Lys Asp Leu Glu Gly Asp Gly Leu Ala Asp Val Ala
565 570 575

Val Gly Ala Glu Ser Gln Met Ile Val Leu Ser Ser Arg Pro Val Val
580 585 590

Asp Met Val Thr Leu Met Ser Phe Ser Pro Ala Glu Ile Pro Val His
595 600 605

Glu Val Glu Cys Ser Tyr Ser Thr Ser Asn Lys Met Lys Glu Gly Val
610 615 620

Asn Ile Thr Ile Cys Phe Gln Ile Lys Ser Leu Tyr Pro Gln Phe Gln
625 630 635 640

Gly Arg Leu Val Ala Asn Leu Thr Tyr Thr Leu Gln Leu Asp Gly His
645 650 655

Arg Thr Arg Arg Arg Gly Leu Phe Pro Gly Gly Arg His Glu Leu Arg
660 665 670

Arg Asn Ile Ala Val Thr Thr Ser Met Ser Cys Thr Asp Phe Ser Phe
675 680 685

His Phe Pro Val Cys Val Gln Asp Leu Ile Ser Pro Ile Asn Val Ser
690 695 700

Leu Asn Phe Ser Leu Trp Glu Glu Glu Gly Thr Pro Arg Asp Gln Arg
705 710 715 720

Ala Gln Gly Lys Asp Ile Pro Pro Ile Leu Arg Pro Ser Leu His Ser
725 730 735

Glu Thr Trp Glu Ile Pro Phe Glu Lys Asn Cys Gly Glu Asp Lys Lys
740 745 750

Cys Glu Ala Asn Leu Arg Val Ser Phe Ser Pro Ala Arg Ser Arg Ala
755 760 765

Leu Arg Leu Thr Ala Phe Ala Ser Leu Ser Val Glu Leu Ser Leu Ser
770 775 780

Asn Leu Glu Glu Asp Ala Tyr Trp Val Gln Leu Asp Leu His Phe Pro
785 790 795 800

Pro Gly Leu Ser Phe Arg Lys Val Glu Met Leu Lys Pro His Ser Gln
805 810 815

Ile Pro Val Ser Cys Glu Glu Leu Pro Glu Glu Ser Arg Leu Leu Ser
820 825 830

Arg Ala Leu Ser Cys Asn Val Ser Ser Pro Ile Phe Lys Ala Gly His
835 840 845

Ser Val Ala Leu Gln Met Asn Phe Asn Thr Leu Val Asn Ser Ser Trp
850 855 860

Gly Asp Ser Val Glu Leu His Ala Asn Val Thr Cys Asn Asn Glu Asp
865 870 875 880

Ser Asp Leu Leu Glu Asp Asn Ser Ala Thr Thr Ile Ile Pro Ile Leu
885 890 895

Tyr Pro Ile Asn Ile Leu Ile Gln Asp Gln Glu Asp Ser Thr Leu Tyr
900 905 910

Val Ser Phe Thr Pro Lys Gly Pro Lys Ile His Gln Val Lys His Met
915 920 925

Tyr Gln Val Arg Ile Gln Pro Ser Ile His Asp His Asn Ile Pro Thr
930 935 940

Leu Glu Ala Val Val Gly Val Pro Gln Pro Pro Ser Glu Gly Pro Ile
945 950 955 960

Thr His Gln Trp Ser Val Gln Met Glu Pro Pro Tyr Pro Cys His Tyr
965 970 975

Glu Asp Leu Glu Arg Leu Pro Asp Ala Ala Glu Pro Cys Leu Pro Gly
980 985 990

Ala Leu Phe Arg Cys Pro Val Val Phe Arg Gln Glu Ile Leu Val Gln
995 1000 1005

Val Ile Gly Thr Leu Glu Leu Val Gly Glu Ile Glu Ala Ser Ser Met
1010 1015 1020

Phe Ser Leu Cys Ser Ser Leu Ser Ile Ser Phe Asn Ser Ser Lys His
1025 1030 1035 1040

Phe His Leu Tyr Gly Ser Asn Ala Ser Leu Ala Gln Val Val Met Lys
1045 1050 1055

Val Asp Val Val Tyr Glu Lys Gln Met
1060 1065

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 676 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Gln Glu Cys Thr Lys Phe Lys Val Ser Ser Cys Arg Glu Cys Ile Glu
1 5 10 15

Ser Gly Pro Gly Cys Thr Trp Cys Gln Lys Leu Asn Phe Thr Gly Pro
20 25 30

Gly Asp Pro Asp Ser Ile Arg Cys Asp Thr Arg Pro Gln Leu Leu Met
35 40 45

Arg Gly Cys Ala Ala Asp Asp Ile Met Asp Pro Thr Ser Leu Ala Glu
50 55 60

Thr Gln Glu Asp His Asn Gly Gly Gln Lys Gln Leu Ser Pro Gln Lys
65 70 75 80

Val Thr Leu Tyr Leu Arg Pro Gly Gln Ala Ala Ala Phe Asn Val Thr
85 90 95

Phe Arg Arg Ala Lys Gly Tyr Pr Ile Asp Leu Tyr Tyr Leu Met Asp
100 105 110

Leu Ser Tyr Ser Met Leu Asp Asp Leu Arg Asn Val Lys Lys Leu Gly
115 120 125

Gly Asp Leu Leu Arg Ala Leu Asn Glu Ile Thr Glu Ser Gly Arg Ile
130 135 140

Gly Phe Gly Ser Phe Val Asp Lys Thr Val Leu Pro Phe Val Asn Thr
145 150 155 160

His Pro Asp Lys Leu Arg Asn Pro Cys Pro Asn Lys Glu Lys Glu Cys
165 170 175

Gln Pro Pro Phe Ala Phe Arg His Val Leu Lys Leu Thr Asn Asn Ser
180 185 190

Asn Gln Phe Gln Thr Glu Val Gly Lys Gln Leu Ile Ser Gly Asn Leu
195 200 205

Asp Ala Pro Glu Gly Gly Leu Asp Ala Met Met Gln Val Ala Ala Cys
210 215 220

Pro Glu Glu Ile Gly Asn Arg Asn Val Thr Arg Leu Leu Val Phe Ala
225 230 235 240

Thr Asp Asp Gly Phe His Phe Ala Gly Asp Gly Lys Leu Gly Ala Ile
245 250 255

Leu Thr Pro Asn Asp Gly Arg Cys His Leu Glu Asp Asn Leu Tyr Lys
260 265 270

Arg Ser Asn Glu Phe Asp Tyr Pro Ser Val Gly Gln Leu Ala His Lys
275 280 285

Leu Ala Glu Asn Asn Ile Gln Pro Ile Phe Ala Val Thr Ser Arg Met
290 295 300

Val Lys Thr Tyr Glu Lys Leu Thr Glu Ile Ile Pro Lys Ser Ala Val
305 310 315 320

Gly Glu Leu Ser Glu Asp Ser Ser Asn Val Val His Leu Ile Lys Asn
325 330 335

Ala Tyr Asn Lys Leu Ser Ser Arg Val Phe Leu Asp His Asn Ala Leu
340 345 350

Pro Asp Thr Leu Lys Val Thr Tyr Asp Ser Phe Cys Ser Asn Gly Val
355 360 365

```
Thr His Arg Asn Gln Pro Arg Gly Asp Cys Asp Gly Val Gln Ile Asn
 370                 375                 380

Val Pro Ile Thr Phe Gln Val Lys Val Thr Ala Thr Glu Cys Ile Gln
385                 390                 395                 400

Glu Gln Ser Phe Val Ile Arg Ala Leu Gly Phe Thr Asp Ile Val Thr
                405                 410                 415

Val Gln Val Leu Pro Gln Cys Glu Cys Arg Cys Arg Asp Gln Ser Arg
            420                 425                 430

Asp Arg Ser Leu Cys His Gly Lys Gly Phe Leu Glu Cys Gly Ile Cys
        435                 440                 445

Arg Cys Asp Thr Gln Tyr Ile Gly Lys Asn Cys Glu Cys Gln Thr Gln
    450                 455                 460

Gly Arg Ser Ser Gln Glu Leu Glu Gly Ser Cys Arg Lys Asp Asn Asn
465                 470                 475                 480

Ser Ile Ile Cys Ser Gly Leu Gly Asp Cys Val Cys Gly Gln Cys Leu
                485                 490                 495

Cys His Thr Ser Asp Val Pro Gly Lys Leu Ile Tyr Gly Gln Tyr Cys
            500                 505                 510

Glu Cys Asp Thr Ile Asn Cys Glu Arg Tyr Asn Gly Gln Val Cys Gly
        515                 520                 525

Gly Pro Gly Arg Gly Leu Cys Phe Cys Gly Lys Cys Arg Cys His Pro
    530                 535                 540

Gly Phe Glu Gly Ser Ala Cys Gln Cys Glu Arg Thr Thr Glu Gly Cys
545                 550                 555                 560

Leu Asn Pro Arg Arg Val Glu Cys Ser Gly Arg Gly Arg Cys Arg Cys
                565                 570                 575

Asn Val Cys Glu Cys His Ser Gly Tyr Gln Leu Pro Leu Cys Gln Glu
            580                 585                 590

Cys Pro Gly Cys Pro Ser Cys Gly Lys Tyr Ile Ser Cys Ala Glu Cys
        595                 600                 605

Leu Lys Phe Glu Lys Gly Pro Phe Gly Lys Asn Cys Ser Ala Ala Cys
    610                 615                 620

Pro Gly Leu Gln Leu Ser Asn Asn Pro Val Lys Gly Arg Thr Cys Lys
625                 630                 635                 640

Glu Arg Asp Ser Glu Gly Cys Trp Val Ala Tyr Thr Leu Glu Gln Gln
                645                 650                 655
```

Asp Gly Met Asp Arg Tyr Leu Ile Tyr Val Asp Glu Ser Arg Glu Cys
660 665 670

Val Ala Gly Pro
675

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 169 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Thr Pro Ala Pro Lys Ser Cys Pro Glu Arg His Tyr Trp Ala Gln Gly
1 5 10 15

Lys Leu Cys Cys Gln Met Cys Glu Pro Gly Thr Phe Leu Val Lys Asp
20 25 30

Cys Gln His Arg Lys Ala Ala Gln Cys Asp Pro Cys Ile Pro Gly Val
35 40 45

Ser Phe Ser Asp Pro His His Thr Arg Pro His Cys Glu Ser Cys Arg
50 55 60

His Cys Asn Ser Gly Leu Leu Val Arg Asn Cys Ile Thr Ala Asn Ala
65 70 75 80

Glu Cys Ala Cys Arg Asn Gly Trp Gln Cys Arg Asp Lys Glu Cys Thr
85 90 95

Glu Cys Asp Pro Leu Pro Asn Pro Ser Leu Thr Ala Arg Ser Ser Gln
100 105 110

Ala Leu Ser Pro His Pro Gln Pro Thr His Leu Pro Tyr Val Ser Glu
115 120 125

Met Leu Glu Ala Ser Thr Ala Gly His Met Gln Thr Leu Ala Asp Phe
130 135 140

Arg Gln Leu Pro Ala Arg Thr Leu Ser Thr His Trp Pro Pro Gln Arg
145 150 155 160

Ser Leu Cys Ser Ser Asp Phe Ile Arg
165

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 319 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Asp Ala Leu Gly Ser Thr Thr Ala Val Gln Thr Pro Thr Ser Gly Glu
1               5                  10                  15

Pro Leu Val Ser Thr Ser Glu Pro Leu Ser Ser Lys Met Tyr Thr Thr
            20                  25                  30

Ser Ile Thr Ser Asp Pro Lys Ala Asp Ser Thr Gly Asp Gln Thr Ser
        35                  40                  45

Ala Leu Pro Pro Ser Thr Ser Ile Asn Glu Gly Ser Pro Leu Trp Thr
    50                  55                  60

Ser Ile Gly Ala Ser Thr Gly Ser Pro Leu Pro Glu Pro Thr Thr Tyr
65                  70                  75                  80

Gln Glu Val Ser Ile Lys Met Ser Ser Val Pro Gln Glu Thr Pro His
                85                  90                  95

Ala Thr Ser His Pro Ala Val Pro Ile Thr Ala Asn Ser Leu Gly Ser
            100                 105                 110

His Thr Val Thr Gly Gly Thr Ile Thr Thr Asn Ser Pro Glu Thr Ser
        115                 120                 125

Ser Arg Thr Ser Gly Ala Pro Val Thr Thr Ala Ala Ser Ser Leu Glu
    130                 135                 140

Thr Ser Arg Gly Thr Ser Gly Pro Pro Leu Thr Met Ala Thr Val Ser
145                 150                 155                 160

Leu Glu Thr Ser Lys Gly Thr Ser Gly Pro Pro Val Thr Met Ala Thr
                165                 170                 175

Asp Ser Leu Glu Thr Ser Thr Gly Thr Thr Gly Pro Pro Val Thr Met
            180                 185                 190

Thr Thr Gly Ser Leu Glu Pro Ser Ser Gly Ala Ser Gly Pro Gln Val
        195                 200                 205

Ser Ser Val Lys Leu Ser Thr Met Met Ser Pro Thr Thr Ser Thr Asn
    210                 215                 220

Ala Ser Thr Val Pro Phe Asn Pro Asp Glu Asn Ser Arg Gly Met Leu
225                 230                 235                 240
```

Pr Val Ala Val Leu Val Ala Leu Leu Ala Val Ile Val Leu Val Ala
245 250 255

Leu Leu Leu Leu Trp Arg Arg Arg Gln Lys Arg Arg Thr Gly Ala Leu
260 265 270

Val Leu Ser Arg Gly Gly Lys Arg Asn Gly Val Val Asp Ala Trp Ala
275 280 285

Gly Pro Ala Gln Val Pro Glu Glu Gly Ala Val Thr Val Thr Val Gly
290 295 300

Gly Ser Gly Gly Asp Lys Gly Ser Gly Phe Pro Asp Gly Glu Gly
305 310 315

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 553 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: Domain
(B) LOCATION: 1..74
(D) OTHER INFORMATION: /note= "product of exon A"

(ix) FEATURE:
(A) NAME/KEY: Domain
(B) LOCATION: 75..122
(D) OTHER INFORMATION: /note= "product of exon B"

(ix) FEATURE:
(A) NAME/KEY: Domain
(B) LOCATION: 123..170
(D) OTHER INFORMATION: /note= "product of exon C"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Gln Ser Pro Thr Pro Ser Pro Thr Gly Leu Thr Thr Ala Lys Met Pro
1 5 10 15

Ser Trp Pro Leu Ser Ser Asp Pro Leu Pro Thr His Thr Thr Ala Phe
20 25 30

Ser Pro Ala Ser Thr Phe Glu Arg Glu Asn Asp Phe Ser Glu Thr Thr
35 40 45

Thr Ser Leu Ser Pro Asp Asn Thr Ser Thr Gln Val Ser Pro Asp Ser
50 55 60

```
Leu Asp Asn Ala Ser Ala Phe Asn Thr Thr Gly Val Ser Ser Val Gln
65                  70                  75                  80

Thr Pro His Leu Pro Thr His Ala Asp S r Gln Thr Pro Ser Ala Gly
                85                  90                  95

Thr Asp Thr Gln Thr Phe Ser Gly Ser Ala Ala Asx Ala Lys Leu Asn
            100                 105                 110

Pro Thr Pro Gly Ser Asn Ala Ile Ser Asp Val Pro Gly Glu Arg Ser
        115                 120                 125

Thr Ala Ser Thr Phe Pro Thr Asp Pro Val Ser Pro Leu Thr Thr Thr
    130                 135                 140

Leu Ser Leu Ala His His Ser Ser Ala Ala Leu Pro Ala Arg Thr Ser
145                 150                 155                 160

Asn Thr Thr Ile Thr Ala Asn Thr Ser Asp Ala Tyr Leu Asn Ala Ser
                165                 170                 175

Glu Thr Thr Thr Leu Ser Pro Ser Gly Ser Ala Val Ile Ser Thr Thr
            180                 185                 190

Thr Ile Ser Thr Thr Pro Ser Lys Pro Thr Cys Asp Glu Lys Tyr Ala
        195                 200                 205

Asn Ile Thr Val Asp Tyr Leu Tyr Asn Lys Glu Thr Lys Leu Phe Thr
    210                 215                 220

Ala Lys Leu Asn Val Asn Glu Asn Val Glu Cys Gly Asn Asn Thr Cys
225                 230                 235                 240

Thr Asn Asn Glu Val His Asn Leu Thr Glu Cys Lys Asn Ala Ser Val
                245                 250                 255

Ser Ile Ser His Asn Ser Cys Thr Ala Pro Asp Lys Thr Leu Ile Leu
            260                 265                 270

Asp Val Pro Pro Gly Val Glu Lys Phe Gln Leu His Asp Cys Thr Gln
        275                 280                 285

Val Glu Lys Ala Asp Thr Thr Ile Cys Leu Lys Trp Lys Asn Ile Glu
    290                 295                 300

Thr Phe Thr Cys Asp Thr Gln Asn Ile Thr Tyr Arg Phe Gln Cys Gly
305                 310                 315                 320

Asn Met Ile Phe Asp Asn Lys Glu Ile Lys Leu Glu Asn Leu Glu Pro
                325                 330                 335

Glu His Glu Tyr Lys Cys Asp Ser Glu Ile Leu Tyr Asn Asn His Lys
            340                 345                 350
```

```
Phe Thr Asn Ala Ser Lys Ile Ile Lys Thr Asp Phe Gly Ser Pro Gly
        355                 360                 365

Glu Pr  Gln Ile Ile Phe Cys Arg Ser Glu Ala Ala His Gln Gly Val
    370                 375                 380

Ile Thr Trp Asn Pro Pro Gln Arg Ser Phe His Asn Phe Thr Leu Cys
385                 390                 395                 400

Tyr Ile Lys Glu Thr Glu Lys Asp Cys Leu Asn Leu Asp Lys Asn Leu
                405                 410                 415

Ile Lys Tyr Asp Leu Gln Asn Leu Lys Pro Tyr Thr Lys Tyr Val Leu
            420                 425                 430

Ser Leu His Ala Tyr Ile Ile Ala Lys Val Gln Arg Asn Gly Ser Ala
        435                 440                 445

Ala Met Cys His Phe Thr Thr Lys Ser Ala Pro Pro Ser Gln Val Trp
    450                 455                 460

Asn Met Thr Val Ser Met Thr Ser Asp Asn Ser Met His Val Lys Cys
465                 470                 475                 480

Arg Pro Pro Arg Asp Arg Asn Gly Pro His Glu Arg Tyr His Leu Glu
                485                 490                 495

Val Glu Ala Gly Asn Thr Lys Val Arg Asn Glu Ser His Lys Asn Cys
            500                 505                 510

Asp Phe Arg Val Lys Asp Leu Gln Tyr Ser Thr Asp Tyr Thr Phe Lys
        515                 520                 525

Ala Tyr Phe His Asn Gly Asp Tyr Pro Gly Glu Pro Phe Ile Leu His
    530                 535                 540

His Ser Thr Ser Tyr Asn Ser Lys Ala
545                 550
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 194 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Gln Gly His Leu Val His Met Thr Val Val Ser Gly Ser Asn Val Thr
1               5                   10                  15
```

Leu Asn Ile Ser Glu Ser Leu Pro Glu Asn Tyr Lys Gln Leu Thr Trp
20 25 30

Phe Tyr Thr Phe Asp Gln Lys Ile Val Glu Trp Asp Ser Arg Lys Ser
35 40 45

Lys Tyr Phe Glu Ser Lys Phe Lys Gly Arg Val Arg Leu Asp Pro Gln
50 55 60

Ser Gly Ala Leu Tyr Ile Ser Lys Val Gln Lys Glu Asp Asn Ser Thr
65 70 75 80

Tyr Ile Met Arg Val Leu Lys Lys Thr Gly Asn Glu Gln Glu Trp Lys
85 90 95

Ile Lys Leu Gln Val Leu Asp Pro Val Pro Lys Pro Val Ile Lys Ile
100 105 110

Glu Lys Ile Glu Asp Met Asp Asp Asn Cys Tyr Leu Lys Leu Ser Cys
115 120 125

Val Ile Pro Gly Glu Ser Val Asn Tyr Thr Trp Tyr Gly Asp Lys Arg
130 135 140

Pro Phe Pro Lys Glu Leu Gln Asn Ser Val Leu Glu Thr Thr Leu Met
145 150 155 160

Pro His Asn Tyr Ser Arg Cys Tyr Thr Cys Gln Val Ser Asn Ser Val
165 170 175

Ser Ser Lys Asn Gly Thr Val Cys Leu Ser Pro Pro Cys Thr Leu Ala
180 185 190

Arg Ser

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 208 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Val Ile His Val Thr Lys Glu Val Lys Glu Val Ala Thr Leu Ser Cys
1 5 10 15

Gly His Asn Val Ser Val Glu Glu Leu Ala Gln Thr Arg Ile Tyr Trp
20 25 30

Gln Lys Glu Lys Lys Met Val Leu Thr Met Met Ser Gly Asp Met Asn
35 40 45

Ile Trp Pr Glu Tyr Lys Asn Arg Thr Ile Phe Asp Ile Thr Asn Asn
50 55 60

Lys Ser Ile Val Ile Leu Ala Leu Arg Pro Ser Asp Glu Gly Thr Tyr
65 70 75 80

Glu Cys Val Val Leu Lys Tyr Glu Lys Asp Ala Phe Lys Arg Glu His
85 90 95

Leu Ala Glu Val Thr Leu Ser Val Lys Ala Asp Phe Pro Thr Pro Ser
100 105 110

Ile Ser Asp Phe Glu Ile Pro Thr Ser Asn Ile Arg Arg Ile Ile Cys
115 120 125

Ser Thr Ser Gly Gly Phe Pro Glu Pro His Leu Ser Trp Leu Lys Arg
130 135 140

Glu His Leu Ala Glu Val Ile Asn Thr Thr Val Ser Gln Asp Pro Glu
145 150 155 160

Thr Glu Leu Tyr Ala Val Ser Ser Lys Leu Asp Phe Asn Met Thr Thr
165 170 175

Asn His Ser Phe Met Cys Leu Ile Lys Tyr Gly His Leu Arg Val Asn
180 185 190

Gln Thr Phe Asn Trp Asn Thr Thr Lys Gln Glu His Phe Pro Asp Asn
195 200 205

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 74 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Lys Ser Phe Leu Leu Phe Leu Thr Ile Ile Leu Leu Val Val Ile
1 5 10 15

Gln Ile Gln Thr Gly Ser Leu Gly Gln Ala Thr Thr Ala Ala Ser Gly
20 25 30

Thr Asn Lys Asn Ser Thr Ser Thr Lys Lys Thr Pro Leu Lys Ser Gly
35 40 45

Ala Ser Ser Ile Ile Asp Ala Gly Ala Cys Ser Phe Leu Phe Phe Ala
50 55 60

Asn Thr Leu Met Cys Leu Phe Tyr Leu Ser
65 70

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 410 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Asn Lys Val Val Leu Gly Lys Lys Gly Asp Thr Val Glu Leu Thr Cys
1 5 10 15

Thr Ala Ser Gln Lys Lys Ser Ile Gln Phe His Trp Lys Asn Ser Asn
20 25 30

Gln Ile Lys Ile Leu Gly Asn Gln Gly Ser Phe Leu Thr Lys Gly Pro
35 40 45

Ser Lys Leu Asn Asp Arg Ala Asp Ser Arg Arg Ser Leu Trp Asp Gln
50 55 60

Gly Asn Phe Pro Leu Ile Ile Lys Asn Leu Lys Ile Glu Asp Ser Asp
65 70 75 80

Thr Tyr Ile Cys Glu Val Glu Asp Gln Lys Glu Glu Val Gln Leu Leu
85 90 95

Val Phe Gly Leu Thr Ala Asn Ser Asp Thr His Leu Leu Gln Gly Gln
100 105 110

Ser Leu Thr Leu Thr Leu Glu Ser Pro Pro Gly Ser Ser Pro Ser Val
115 120 125

Gln Cys Arg Ser Pro Arg Gly Lys Asn Ile Gln Gly Gly Lys Thr Leu
130 135 140

Ser Val Ser Gln Leu Glu Leu Gln Asp Ala Gly Thr Trp Ile Cys Thr
145 150 155 160

Val Leu Gln Asn Gln Lys Lys Val Glu Phe Lys Ile Asp Ile Val Val
165 170 175

Leu Ala Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys
180 185 190

```
Cys Pro Ala Pro Asn Leu Leu  ly Gly Pro Ser Val Phe Ile Phe Pro
        195                 200                 205

Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr
    210                 215                 220

Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser
225                 230                 235                 240

Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His
                245                 250                 255

Arg Glu Asp Tyr Asn Ser Arg Leu Arg Val Val Ser Ala Leu Pro Ile
            260                 265                 270

Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn
        275                 280                 285

Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys
    290                 295                 300

Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu
305                 310                 315                 320

Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met
                325                 330                 335

Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu
            340                 345                 350

Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe
        355                 360                 365

Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn
    370                 375                 380

Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr
385                 390                 395                 400

Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
                405                 410
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 418 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Lys Glu Ile Thr Asn Ala Leu Glu Thr Trp Gly Ala Leu Gly Gln Asp
1 5 10 15

Ile Asn Leu Asp Ile Pro Ser Phe Gln Met Ser Asp Asp Ile Asp Asp
20 25 30

Ile Lys Trp Glu Lys Thr Ser Asp Lys Lys Lys Ile Ala Gln Phe Arg
35 40 45

Lys Glu Lys Glu Thr Phe Lys Glu Lys Asp Thr Tyr Lys Leu Phe Lys
50 55 60

Asn Gly Thr Leu Lys Ile Lys His Leu Lys Thr Asp Asp Gln Asp Ile
65 70 75 80

Tyr Lys Val Ser Ile Tyr Asp Thr Lys Gly Lys Asn Val Leu Glu Lys
85 90 95

Ile Phe Asp Leu Lys Ile Gln Glu Arg Val Ser Lys Pro Lys Ile Ser
100 105 110

Trp Thr Cys Ile Asn Thr Thr Leu Thr Cys Glu Val Met Asn Gly Thr
115 120 125

Asp Pro Glu Leu Asn Leu Tyr Gln Asp Gly Lys His Leu Lys Leu Ser
130 135 140

Gln Arg Val Ile Thr His Lys Trp Ile Thr Ser Leu Ser Ala Lys Phe
145 150 155 160

Lys Cys Thr Ala Gly Asn Lys Val Ser Lys Glu Ser Ser Val Glu Pro
165 170 175

Val Ser Cys Pro Glu Lys Gly Leu Asp Glu Pro Arg Gly Pro Thr Ile
180 185 190

Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly
195 200 205

Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile
210 215 220

Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp
225 230 235 240

Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His
245 250 255

Thr Ala Gln Thr Ala Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg
260 265 270

Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys
275 280 285

Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu
290 295 300

Glu Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr
305 310 315 320

Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
325 330 335

Thr Cys Met Val Thr Asp Phe Asn Pro Glu Asp Ile Tyr Val Glu Trp
340 345 350

Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val
355 360 365

Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
370 375 380

Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
385 390 395 400

Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
405 410 415

Gly Lys

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 367 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr Asp Asn
1 5 10 15

Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser Arg Glu
20 25 30

Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu Val Cys
35 40 45

Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser Lys Thr
50 55 60

Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr Phe Tyr
65 70 75 80

Leu Gln Asn Leu Tyr Tyr Asn Gln Thr Asp Ile Tyr Phe Cys Lys Ile
85 90 95

Glu Tyr Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn Gly
100 105 110

Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu Phe
115 120 125

Pro Gly Pro Ser Lys Pro Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys
130 135 140

Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val
145 150 155 160

Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser
165 170 175

Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp
180 185 190

Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln
195 200 205

Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser
210 215 220

Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys
225 230 235 240

Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile
245 250 255

Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro
260 265 270

Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met
275 280 285

Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn
290 295 300

Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser
305 310 315 320

Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn
325 330 335

Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu
340 345 350

His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
355 360 365

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 357 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15

Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30

Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45

Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60

Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80

Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95

Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Ala Gln Ile
100 105 110

Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Glu Pro Arg Gly
115 120 125

Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu
130 135 140

Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val
145 150 155 160

Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val
165 170 175

Ser Glu Asp Asp Leu Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val
180 185 190

Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser
195 200 205

Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met
210 215 220

Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pr Ala
225 230 235 240

Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro
245 250 255

Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln
260 265 270

Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr
275 280 285

Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr
290 295 300

Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
305 310 315 320

Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser
325 330 335

Val Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser
340 345 350

Arg Thr Pro Gly Lys
355

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 378 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Pro Pro Glu Lys Lys Glu Leu Arg Lys Val Ala His Leu Thr Gly Lys
1 5 10 15

Ser Asn Ser Arg Ser Met Pro Leu Glu Trp Glu Asp Thr Tyr Gly Ile
20 25 30

Val Leu Leu Ser Gly Val Lys Tyr Lys Lys Gly Gly Leu Val Ile Asn
35 40 45

Glu Thr Gly Leu Tyr Phe Val Tyr Ser Lys Val Tyr Phe Arg Gly Gln
50 55 60

Ser Cys Asn Asn Leu Pro Leu Ser His Lys Val Tyr Met Arg Asn Ser
65 70 75 80

Lys Tyr Pr Gln Asp Leu Val Met Met Glu Gly Lys Met Met Ser Tyr
85 90 95

Cys Thr Thr Gly Gln Met Trp Ala Arg Ser Ser Tyr Lys Gly Ala Val
100 105 110

Phe Asn Leu Thr Ser Ala Asp His Leu Tyr Val Asn Val Ser Glu Leu
115 120 125

Ser Leu Val Asn Phe Glu Glu Ser Gln Thr Phe Phe Gly Leu Tyr Lys
130 135 140

Leu Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys
145 150 155 160

Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro
165 170 175

Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys
180 185 190

Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp
195 200 205

Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg
210 215 220

Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln
225 230 235 240

His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn
245 250 255

Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly
260 265 270

Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu
275 280 285

Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met
290 295 300

Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu
305 310 315 320

Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe
325 330 335

Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn
340 345 350

Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr
355 360 365

Thr Lys Ser Phe Ser Arg Thr Pr Gly Lys
370 375

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..33
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGCTCTAGAA TGAGCTTTCC ATGTAAATTT GTA
33

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..36
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TGTGGGCCCT CTGGGCTCGT CCAGACCTTT CTCTGG
36

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..27
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CGCTCTAGAA TGAACCGGGG AGTCCCT
27

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..34
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GGGCCCTCTG GGCTCAGCTA GCACCACGAT GTCT
34

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..35
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CCAGAGAAAG GTCTGGACGA GCCCAGAGGG CCCAC
35

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..34
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AGACATCGTG GTGCTAGCTG AGCCCAGAGG GCCC
34

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..33
(D) OTHER INFORMATION: /label= primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGCGAATTCT TTACCCGGAG TCCGGGAGAA GCT
33

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..25
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met Asn Arg Gly Val Pro Phe Arg His Leu Leu Leu Val Leu Gln L u
1 5 10 15

Ala Leu Leu Pro Ala Ala Thr Gln Gly
20 25

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..24
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Ser Phe Pro Cys Lys Phe Val Ala Ser Phe Leu Leu Ile Phe Asn
1 5 10 15

Val Ser Ser Lys Gly Ala Val Ser
20

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..18
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1 5 10 15

Thr Gly

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..37
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Ala Cys Leu Gly Phe Gln Arg His Lys Ala Gln Leu Asn Leu Ala
1 5 10 15

Thr Arg Thr Trp Pro Cys Thr Leu Leu Phe Phe Leu Leu Phe Ile Pro
20 25 30

Val Phe Cys Lys Ala
35

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..24
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Pro Met Gly Ser Leu Gln Pro Leu Ala Thr Leu Tyr Leu Leu Gly
1 5 10 15

Met Leu Val Ala Ser Cys Leu Gly
20

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATI N: 1..25
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Ala Gly Pro Pro Arg Leu Leu Leu Leu Pro Leu Leu Leu Ala Leu
1 5 10 15

Ala Arg Gly Leu Pro Gly Ala Leu Ala
20 25

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..26
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Met Lys Asp Ser Cys Ile Thr Val Met Ala Met Ala Leu Leu Ser Gly
1 5 10 15

Phe Phe Phe Phe Phe Ala Pro Ala Ser Ser
20 25

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..22
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Leu Gly Leu Arg Pro Pro Leu Leu Ala Leu Val Gly Leu Leu Ser
1 5 10 15

Leu Gly Cys Val Leu Ser
20

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..20
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Met Ala Arg Pro His Pro Trp Trp Leu Cys Val Leu Gly Thr Leu Val
1 5 10 15

Gly Leu Ser Ala
20

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..15
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Met Ala Thr Leu Leu Leu Leu Leu Gly Val Leu Val Val Ser Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..23
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp
1 5 10 15

Thr Glu Val Phe Val Thr Gly
20

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..26
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Met Trp Ser Arg Gly Trp Asp Ser Cys Leu Ala Leu Glu Leu Leu Leu
1 5 10 15

Leu Pro Leu Ser Leu Leu Val Thr Ser Ile
20 25

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 1..34
(D) OTHER INFORMATION: /label= leader

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Met	Gly	His	Thr	Arg	Arg	Gln	Gly	Thr	Ser	Pro	Ser	Lys	Cys	Pro	Tyr
1				5					10					15	

Leu	Asn	Phe	Phe	Gln	Leu	Leu	Val	Leu	Ala	Gly	Leu	Ser	His	Phe	Cys
			20					25					30		

Ser Gly

While various embodiments of the present invention have been described in detail, it is apparent that modifications and adaptations of those embodiments will occur to those skilled in the art. It is to be expressly understood, however, that such modifications and adaptations are within the scope of the present invention, as set forth in the following claims:

What is claimed is:

1. A T lymphocyte veto molecule comprising a chimeric molecule having a protein selected from the group consisting of CD4 protein, CD2 protein, CD28 protein, CTLA4 protein, Fas-ligand protein, CD5 protein, CD7 protein, CD9 protein, CD11 protein, CD18 protein, CD27 protein, CD43 protein, CD45 protein, CD48 protein, B7.1 protein and B7.2 protein, wherein said protein is linked to a targeting polypeptide that binds to a molecule that differentiates a host cell from a tissue graft cell.

2. The veto molecule of Claim 1, wherein said chimeric molecule is derived from an animal selected from the group consisting of a human, a non-human primate, a pig, a mouse, a rat, a rabbit, a horse, a goat and a hamster.

3. The veto molecule of Claim 1, wherein said chimeric molecule is derived from an animal selected from the group consisting of a human, a baboon and a pig.

4. The veto molecule of Claim 1, wherein said protein is a CD4 protein that comprises at least one V and at least one C2 domain of a CD4 protein.

5. The veto molecule of Claim 1, wherein said protein comprises an amino acid substitution comprising a residue selected from the group consisting of proline and cysteine.

6. The veto molecule of Claim 1, wherein said protein is a CD4 protein that comprises the amino acid

sequence extending from about residue 1 to about residue 203 of a CD4 protein, in which the initiating Met is residue 1.

7. The veto molecule of Claim 1, wherein said protein is a CD2 protein that comprises the extracellular domains of a CD2 protein.

8. The veto molecule of Claim 1, wherein said protein is a CD2 protein that comprises the amino acid sequence extending from about residue 1 to about residue 208 of a CD2 protein, in which the initiating Met is residue 1.

9. The veto molecule of Claim 1, wherein said protein is a CD28 protein that comprises a homodimer of the pseudo-V-region of a CD28 protein.

10. The veto molecule of Claim 1, wherein said protein is a CD28 protein that comprises the amino acid sequence extending from about residue 1 to about residue161 of a CD28 protein, in which the initiating Met is residue 1.

11. The veto molecule of Claim 1, wherein said protein is a CTLA4 protein that comprises a homodimer of the pseudo-V-region of a CTL4A protein.

12. The veto molecule of Claim 1, wherein said protein is a CTLA4 protein that comprises the amino acid sequence extending from about residue 1 to about residue 161 of a CTL4A protein, in which the initiating Met is residue 1.

13. The veto molecule of Claim 1, wherein said protein is a Fas-ligand protein that comprises the extracellular domain of a Fas-ligand protein.

14. The veto molecule of Claim 1, wherein said protein is a Fas-ligand protein that comprises the amino acid sequence extending from about residue 137 to about residue 283 of a Fas-ligand protein, in which the initiating Met is residue 1.

15. The veto molecule of Claim 1, wherein said protein is a CD5 protein that comprises domains 1 through 3 of a CD5 protein.

16. The veto molecule of Claim 1, wherein said protein is a CD5 protein that comprises the amino acid sequence extending from about residue 1 to about residue 372 of a CD5 protein, in which the initiating Met is residue 1.

17. The veto molecule of Claim 1, wherein said protein is a CD7 protein that comprises the psuedo-V-region of a CD7 protein.

18. The veto molecule of Claim 1, wherein said protein is a CD7 protein that comprises the amino acid sequence extending from about residue 1 to about residue 180 of a CD7 protein, in which the initiating Met is residue 1.

19. The veto molecule of Claim 1, wherein said protein is a CD9 protein that comprises the extracellular domain of a CD9 protein.

20. The veto molecule f Claim 1, wherein said protein is a CD9 protein that comprises the amino acid sequence extending from about residue 113 to about residue 192 of a CD9 protein, in which the initiating Met is residue 1.

21. The veto molecule of Claim 1, wherein said protein is a CD11 protein that comprises the CD11 alpha domain of a CD11 protein complexed with the CD18 extracellular domain.

22. The veto molecule of Claim 1, wherein said protein is a CD11 protein that comprises the amino acid sequence extending from about residue 1 to about residue 1089 of a CD11 alpha protein, in which the initiating Met is residue 1.

23. The veto molecule of Claim 1, wherein said protein is a CD18 protein that comprises the extracellular domain of a CD18 protein.

24. The veto molecule of Claim 1, wherein said protein is a CD18 protein that comprises the amino acid sequence extending from about residue 1 to about residue 750 of a CD18 protein, in which the initiating Met is residue 1.

25. The veto molecule of Claim 1, wherein said protein is a CD27 protein that comprises the extracellular domain of a CD27 protein.

26. The veto molecule of Claim 1, wherein said protein is a CD27 protein that comprises the amino acid

sequence extending from about residue 1 to about residue 191 f a zCD27 protein, in which the initiating Met is residue 1.

27. The veto molecule of Claim 1, wherein said protein is a CD43 protein that comprises the extracellular domain of a CD43 protein.

28. The veto molecule of Claim 1, wherein said protein is a CD43 protein that comprises the amino acid sequence extending from about residue 1 to about residue 384 of a CD43 protein, in which the initiating Met is residue 1.

29. The veto molecule of Claim 1, wherein said protein is a CD45 protein that comprises an extracellular domain of an isoform of a CD45 protein.

30. The veto molecule of Claim 1, wherein said protein is a CD45 protein that comprises the amino acid sequence extending from about residue 1 to about residue 556 of a CD45 protein, in which the initiating Met is residue 1.

31. The veto molecule of Claim 1, wherein said protein is a CD48 protein that comprises a pseudovariable and a pseudoconstant extracellular domains of a CD48 protein.

32. The veto molecule of Claim 1, wherein said protein is a CD48 protein that comprises the amino acid sequence extending from about residue 1 to about residue

220 of a CD48 protein, in which the initiating Met is residue 1.

33. The v to molecule of Claim 1, wherein said protein is a B7.1 protein that comprises a pseudovariable and a pseudoconstant extracellular domains of a B7.1 protein.

34. The veto molecule of Claim 1, wherein said protein is a B7.1 protein that comprises the amino acid sequence extending from about residue 1 to about residue 242 of a B7.1 protein, in which the initiating Met is residue 1.

35. The veto molecule of Claim 1, wherein said protein is a B7.2 protein that comprises an extracellular domain of a B7.2 protein.

36. The veto molecule of Claim 1, wherein said protein is a B7.2 protein that comprises the amino acid sequence extending from about residue 1 to about residue 74 of a B7.2 protein, in which the initiating Met is residue 1.

37. The veto molecule of Claim 1, wherein said protein comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

38. The vet molecul of Claim 1, wherein said protein is linked by a peptide b nd to the c nstant regi n domain of an immunoglobulin molecule, to form a protein:Ig conjugated molecule.

39. The veto molecule of Claim 38, wherein said immunoglobulin molecule of said protein:Ig conjugated molecule comprises a constant region domain of an IgG2a molecule.

40. The veto molecule of Claim 38, wherein said protein:Ig conjugated molecule comprises an amino acid sequence comprising a sequence selected from the group consisting of SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20 and SEQ ID NO:21.

41. The veto molecule of Claim 1, wherein said targeting polypeptide comprises an immunoglobulin molecule.

42. The veto molecule of Claim 1, wherein said targeting polypeptide comprises an immunoglobulin that binds to a major histocompatibility molecule.

43. The veto molecule of Claim 1, wherein said targeting polypeptide comprises an immunoglobulin molecule selected from the group consisting of WFL4F12.3, WFL3C6.1, BB7.2, PA2.1, 2.28M1, MA2.1, GAP A3, A11.1M, 4D12, BB7.1, B27M1, ME1, BB7.6, MB40.2, MB40.2, B27M2, SFR8-B6, Genox 3.53, G2a.5 and SFR3-DR5.

44. The veto molecule of Claim 1, wherein said protein is linked to said targeting polypeptide by a chemically produced di-sulfide bond.

45. The veto molecule of Claim 1, wherein said chimeric m lecule can be secreted from a cell that produces said molecule.

46. A recombinant cell having: (1) a first recombinant m lecule comprising a first nucleic acid molecule operatively linked to an expression vector, said first nucleic acid molecule having a sequence encoding a first protein selected from the group consisting of CD4, CD2, CD28, CTL4A, Fas-ligand, CD5, CD7, CD9, CD11, CD18, CD27, CD43, CD45, CD48, B7.1 and B7.2; and (2) a second recombinant molecule comprising a second nucleic acid molecule operatively linked to an expression vector, said second nucleic acid molecule having a sequence encoding a second protein comprising a targeting molecule selected from the group consisting of a targeting molecule that differentiates a host cell from a tissue graft cell and a targeting molecule that selectively targets a stimulator cell involved in an autoimmune response.

47. The recombinant cell of Claim 46, wherein said first and second proteins are bound to the plasma membrane of said recombinant cell.

48. The recombinant cell of Claim 46, wherein said recombinant cell is not capable of stimulating a T cell response.

49. The recombinant cell of Claim 46, wherein said recombinant cell is derived from a host cell selected from the group consisting of a fibroblast, a pluripotent progenitor cell, an epithelial cell, a neural cell, a T cell line and a B cell line.

50. The recombinant cell of Claim 46, wherein said first nucleic acid molecule comprises a nucleic acid sequence that enc des an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

51. The recombinant cell of Claim 46, wherein second nucleic acid molecule encodes an amino acid sequence derived from a protein selected from the group consisting of an immunoglobulin molecule, a growth factor and a tissue specific antigen.

52. A composition comprising: a T lymphocyte veto molecul comprising a chimeric molecule having a targeting molecule selected from the group consisting of a targeting molecule that differentiates a host cell from a tissue graft cell and a targeting molecule that selectively targets a stimulator cell involved in an autoimmune response, wherein said targeting molecule is linked to a protein selected from the group consisting of a CD4 protein, a CD2 protein, a CD28 protein, a CTL4A protein, a Fas-ligand protein, a CD5 protein, a CD7 protein, a CD9 protein, a CD11 protein, a CD18 protein, a CD27 protein, a CD43 protein, a CD45 protein, a CD48 protein, a B7.1 protein and a B7.2 protein and mixtures thereof; and a pharmaceutically acceptable carrier.

53. A method for producing a T lymphocyte veto molecule, comprising:

(a) providing a first protein comprising a compound selected from the group consisting of a CD4, CD2, CD28, CTL4A, Fas-ligand, CD5, CD7, CD9, CD11, CD18, CD27, CD43, CD45, CD48, B7.1 and B7.2 protein;

(b) providing a second protein comprising a targeting molecule selected from the group consisting of a targeting molecule that differentiates a host cell from a tissue graft cell and a targeting molecule that selectively targets a stimulator cell involved in an autoimmune response; and

(c) linking said first protein to said second protein to form a chimeric molecule.

54. The method of Claim 53, wherein said first protein is produced by culturing a cell transformed with a recombinant molecule comprising a nucleic acid molecule operatively linked to an expression vector, said nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 and mixtures thereof.

55. The method of Claim 53, wherein said second protein is produced by culturing a cell transformed with a recombinant molecule comprising a nucleic acid mol cule

operatively linked to an expressi n vect r, said nucleic acid m lecule comprising a nucleic acid sequence encoding an amino acid sequence derived from a protein selected from the group consisting of an immunoglobulin molecule, a growth factor and a tissue specific antigen.

56. The method of Claim 53, wherein said step of linking comprises combining said first and second proteins and contacting said proteins with a reagent capable of creating di-sulfide bonds between said first and second proteins.

57. The method of Claim 53, wherein said step of linking is performed using N-succinimidyl-3-1-(1-pyridyldthio)-propionate.

58. The method of Claim 53, wherein said chimeric molecule is recovered from said first and second proteins that have not been linked.

59. The method of Claim 53, wherein said chimeric molecule is recovered from said first and second proteins that have not been linked by a method selected from the group consisting of size separation chromatography, affinity chromatography, ion-exchange chromatography, reverse phase chromatography, chromatofocussing, hydroxyapatite adsorption and electrophoresis systems.

60. A method to suppress an immune response comprising:

(a) providing a chimeric molecule having a protein selected from the group consisting of CD4 protein, CD2 protein, CD28 protein, CTL4A protein, Fas-ligand protein, CD5 protein, CD7 protein, CD9 protein, CD11 protein, CD18 protein, CD27 protein, CD43 protein, CD45 protein, CD48 protein, B7.1 protein and B7.2 protein, wherein said protein is linked to a stimulator cell-targeting molecule; and

(b) exposing said chimeric molecule to a stimulator cell that can interact specifically with said chimeric molecule, for a time and under conditions sufficient to enable said stimulator cell to reduce an immune response of a responder cell.

61. The method of Claim 60, wherein said chimeric molecule is contacted with said stimulator cell *in vivo*.

62. The method of Claim 60, wherein said responder cell is a T cell.

63. The method of Claim 60, wherein said responder cell is a CD4+ T lymphocyte.

64. The method of Claim 60, wherein said immune response is directed against a tissue-graft antigen or a processed antigen.

65. The method of Claim 60, wherein said exposure time is from between about 1 hour to about 4 days.

66. (a) A method to all viate tissue transplant rejection, comprising administering to an animal an effective amount of a therapeutic composition comprising a T lymphocyte veto molecule comprising a chimeric molecule having a targeting molecule that differentiates a host cell from a tissue graft cell, wherein said targeting molecule is linked to a protein selected from the group consisting of a CD4 protein, a CD2 protein, a CD28 protein, a CTL4A protein, a Fas-ligand protein, a CD5 protein, a CD7 protein, a CD9 protein, a CD11 protein, a CD18 protein, a CD27 protein, a CD43 protein, a CD45 protein, a CD48 protein, a B7.1 protein and a B7.2 protein and mixtures thereof.

67. The method of Claim 66, wherein said targeting molecule that differentiates a host cell from a tissue graft cell comprises an immunoglobulin that specifically binds to an epitope on a major histocompatibility complex molecule.

68. The method of Claim 66, wherein said chimeric molecule is administered to said animal prior to and after said animal receives a tissue transplant.

69. The method of Claim 66, wherein said chimeric molecule is administered to said animal in two injections about one week prior to transplantation.

70. The method of Claim 66, wherein said chimeric molecule is administered to said animal about 2 weeks to about 3 weeks after said animal receives a tissue transplant.

71. The method of Claim 66, wherein said therapeutic composition is sterile and further comprises a pharmaceutically acceptable carrier.

72. The method of Claim 66, wherein said therapeutic composition is administered by a method selected from the group consisting of oral, nasal, topical, inhaled, transdermal, rectal, intraarticular, intracranial, intraperitoneal and intravenous routes.

73. The method of Claim 66, wherein said animal is selected from the group consisting of humans, dogs, cats, cows and horses.

74. A T lymphocyte veto molecule comprising a chimeric molecule having a protein selected from the group consisting of CD4 protein, CD2 protein, CD28 protein, CTLA4 protein, Fas-ligand protein, CD5 protein, CD7 protein, CD9 protein, CD11 protein, CD18 protein, CD27 protein, CD43 protein, CD45 protein, CD48 protein, B7.1 protein and B7.2 protein, wherein said protein is linked to a targeting polypeptide that binds to a molecule which selectively targets a stimulator cell involved in an autoimmune response.

75. The veto molecule of Claim 74, wherein said chimeric molecule is derived from an animal selected from the group consisting of a human, a non-human primate, a pig, a mouse, a rat, a rabbit, a horse, a goat and a hamster.

76. The veto molecule of Claim 74, wherein said protein comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

77. The veto molecule of Claim 74, wherein said protein is linked by a peptide bond to the constant region domain of an immunoglobulin molecule, to form a protein:Ig conjugated molecule.

78. The veto molecule of Claim 77, wherein said immunoglobulin molecule of said protein:Ig conjugated molecule comprises a constant r gion domain of an IgG2a molecule.

79. The veto molecule of Claim 77, wherein said protein:Ig conjugated molecule comprises an amino acid sequence comprising a sequence selected from the group consisting of SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20 and SEQ ID NO:21.

80. The veto molecule of Claim 74, wherein said targeting polypeptide is selected from the group consisting of an immunoglobulin molecule, a growth factor and a tissue specific antigen.

81. The veto molecule of Claim 74, wherein said targeting polypeptide comprises an immunoglobulin that binds to a protein selected from the group consisting of a major histocompatibility molecule, asialoglycoprotein receptor, bile acid receptor, LMA surface target molecules, heart cell surface proteins, islets of Langerhans cell surface proteins, c-kit receptor and blood proteins.

82. The veto molecule of Claim 74, wherein said targeting polypeptide comprises an immunoglobulin molecule selected from the group consisting of WFL4F12.3, WFL3C6.1, BB7.2, PA2.1, 2.28M1, MA2.1, GAP A3, A11.1M, 4D12, BB7.1, B27M1, ME1, BB7.6, MB40.2, MB40.2, B27M2, SFR8-B6, Genox 3.53, G2a.5 and SFR3-DR5.

83. The veto molecule of Claim 74, wherein said targeting polypeptide comprises a growth factor selected from the group consisting of thyroid stimulating hormone, vasopressin, or corticotropin.

84. The veto molecule of Claim 74, wherein said targeting polypeptide comprises a tissue specific marker selected from the group consisting of asialoglycoprotein receptor, thyroid stimulating hormone receptor, vasopressin receptor or corticotropin receptor.

85. The veto molecule of Claim 74, wherein said protein is linked to said targeting polypeptide by a chemically produced di-sulfide bond.

86. The veto molecule of Claim 74, wherein said chimeric molecule can be secreted from a cell that produces said molecule.

87. A method to treat an autoimmune disease, comprising administering to an animal an eff ctive amount of a therapeutic composition comprising a chim ric molecule having a targeting molecule which selectively targets a stimulator cell involved in an autoimmune response, wherein said targeting molecule is linked to a protein selected from the group consisting of a CD4 protein, a CD2 protein, a CD28 protein, a CTL4A protein, a Fas-ligand protein, a CD5 protein, a CD7 protein, a CD9 protein, a CD11 protein, a CD18 protein, a CD27 protein, a CD43 protein, a CD45 protein, a CD48 protein, a B7.1 protein and a B7.2 protein, and mixtures thereof.

88. The method of Claim 87, wherein said autoimmune disease selected from the group consisting of systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, insulin-dependent diabetes mellitus, multiple sclerosis, celiac disease, autoimmune thyroiditis, Addison's disease, Graves' disease and rheumatic carditis.

89. The method of Claim 87, wherein said therapeutic composition is sterile and further comprises a pharmaceutically acceptable carrier.

90. The method of Claim 87, wherein said therapeutic composition is administered by a method selected from the group consisting of oral, nasal, topical, inhaled, transdermal, rectal, intraarticular, intracranial, intraperitoneal and intravenous routes.

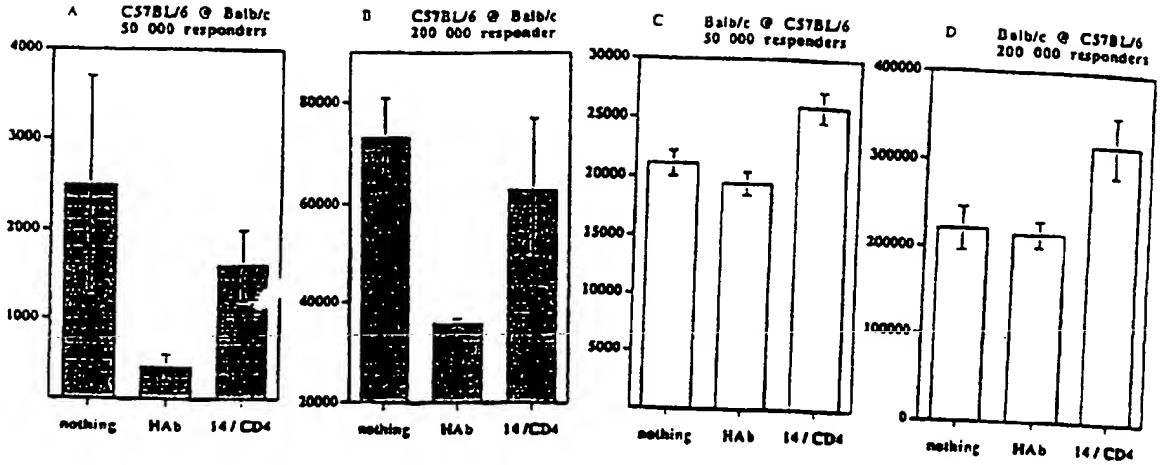
A
C57BL/6 @ Balb/c
50 000 responders
4000
3000
2000
1000
nothing
HAb
14/CD4
B
C57BL/6 @ Balb/c
200 000 responder
80000
60000
40000
20000
nothing
HAb
14/CD4
C
Balb/c @ C57BL/6
50 000 responders
30000
25000
20000
15000
10000
5000
nothing
HAb
14/CD4
D
Balb/c @ C57BL/6
200 000 responders
400000
300000
200000
100000
0
nothing
HAb
14/CD4

Fig. 1

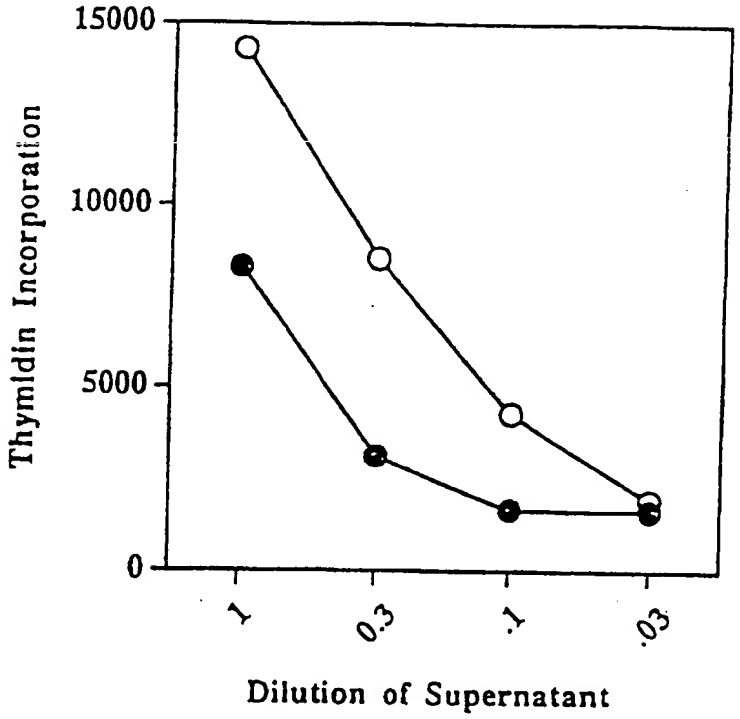
15000
10000
5000
0
Thymidin Incorporation
1
0.3
.1
.03
Dilution of Supernatant

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05943

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 39/395; C12N 5/10, 15/12, 15/13; C12P 21/08

US CL Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U S : 424/130 1, 134 1; 435/69 1, 70.1, 71.1, 172 3, 252.3; 514/8, 885; 530/387 3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG, BIOSIS, EMBASE, MEDLINE, CA, WPI
search terms: cd2, soluble, chimeric, recombinant, immunoglobulin, antibod?, staerz

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,428,130 A (D. J. CAPON ET AL.) 27 June 1995, see entire document.	1-3, 5-8, 37-59, 74-90
Y	WO 90/08187 (DANA FARBER CANCER INSTITUTE) 26 July 1990, see entire document.	1-3, 5-8, 37-59, 74-90
Y	Cell. Immunol., Volume 149, issued 1993, Rabin et al., "Inhibition of T Cell Activation and Adhesion Functions by Soluble CD2 Protein", pages 24-38, see entire document.	1-3, 5-8, 37-59, 74-90

☐ Further documents are listed in the continuation of Box C ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 31 JULY 1997	Date of mailing of the international search report 19 AUG 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PHILLIP GABEL Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05943

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/130.1, 134.1; 435/69.1, 70.1, 71.1, 172.3, 252.3; 514/8, 885; 530/387.3